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THE CLINICAL FEATURES OF HYPERCALCEMIA ASSOCIATED WITH MALIGNANT DISEASE*

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In 1925 Collip[1] reported that in dogs, overdosage with parathyroid hormone resulted in death accompanied by high blood calcium. Associated with the hypercalcemia were "loss of appetite, dullness verging on coma, general atonia and a failing circulation". Subsequent observation in humans has not added greatly to the essential features of this clinical syndrome.

Several early reports suggested an association between hypercalcemia and malignant disease[2-5] but clinical interest was not aroused until the Gutmans,[6] in 1936, emphasized the relatively common occurrence of hypercalcemia in patients with multiple myeloma.

Since 1949, clinicians have become more aware of the relationship between malignant disease and hypercalcemia[7-18] and in most of these patients the reason for hypercalcemia and hypercalcuria seems clear. If osteolytic lesions cause a release of calcium to the kidneys greater than can be excreted, hypercalcemia follows and with continuing hypercalcemia kidney damage and failure may also occur. It is the impression of the present writers, shared by others, that physicians still do not appreciate how frequently hypercalcemia appears as a complication of malignant disease. The purposes of this report are to stress again its relative frequency and to describe our clinical experience with the entity.

About five years ago we became interested in determining how frequently disturbances in calcium metabolism might be occurring in a group of hospital patients suffering from malignant disease. Four hundred and thirty-eight patients were examined at the time of admission to the Toronto General Hospital for radiation therapy. Forty of these patients (9.1%) had serum calcium values above normal. In 1958 the major facilities for radiation therapy were moved to the Princess Margaret Hospital to which over 3000 new patients with malignant disease are admitted annually. In view of the high incidence of hypercalcemia among these patients, estimations of serum calcium and blood urea were done when the patient's symptoms suggested hypercalcemia, when extensive osteolytic disease was present and when therapy was being initiated or altered in patients with breast cancer. This present paper reports our experience with the first 100 cases of hypercalcemia diagnosed within an 18-month period following the opening of this hospital.

With the method in use in our laboratory, the normal range for serum calcium is 9 to 10.5 mg. %.* Borderline cases have been excluded by describing only those patients with serum calcium values of 11 mg. % and higher.

TABLE I.—Hypercalcemia in Association with Malignant Disease

Diagnosis and site of malignancy	*No.*
Breast	65
Multiple myeloma	5
Kidney	5
Bronchus	4
Malignant lymphoma	4
Oral cavity	3
Uterus	2
Thyroid	2
Breast and ovary	2
Acute lymphatic leukemia	1
Brain (astrocytoma)	1
Testicle	1
Ovary	1
Antrum	1
Esophagus	1
Larynx	1
Pharynx	1
Total	100

Observations.—The age range of the 100 patients with hypercalcemia was from 12 to 82 years. Table I shows the various forms of malignant disease in which hypercalcemia was found. Two-thirds of the patients had breast cancer and there was a wide variety of other types of cancer. The last two patients deserve special mention. They

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*Anal. Chem., 25: 1738, 1953. This procedure has been modified as follows: The precipitate is dissolved in two drops of 70% perchloric acid and boiled for one minute. After cooling, 5 ml. of 40% isopropyl alcohol is added. This mixture is burned using the oxyacetylene flame in the Beckman model DU spectrophotometer with photomultiplier attachment, at wave length 622.5. There is a close correlation between the values obtained by this method and those obtained using the method of Campbell (Campbell, W. R.: *Canad. J. Biochem. & Physiol.*, 35: 1033, 1957).

had had complete removal of the thyroid and parathyroid glands during surgery for carcinoma of the larynx and pharynx. The hypercalcemia in these cases was a complication of the therapeutic administration of vitamin D and calcium given to control hypoparathyroidism.

It is of practical interest that 20% of the patients had no clinical or radiological evidence of metastatic bone disease. Not all of these patients, however, had a complete skeletal survey.

TABLE II.—TREATMENT ANTEDATING ONSET OF HYPERCALCEMIA IN BREAST CANCER (65 CASES)

Castration			
(a) Surgical	1		
(b) Radiation	8	9	
Androgen		9	
Radiation therapy		8	
Estrogen		3	
Prednisone withdrawal		1	30
No previous treatment			35

As shown in Table II, only nine of the 65 patients with breast cancer were receiving therapy with male hormone. In 35, no treatment was being given at the time hypercalcemia was observed. In the remaining patients, hypercalcemia was associated with all of the accepted forms of management of breast cancer.

The initial calcium levels of the one hundred patients are shown in Fig. 1. In 55 patients the values were between 11 and 12 mg. %. In the remainder, values ranged up to 18 mg. %.

With regard to the symptoms of hypercalcemia, it should first be emphasized that there is not

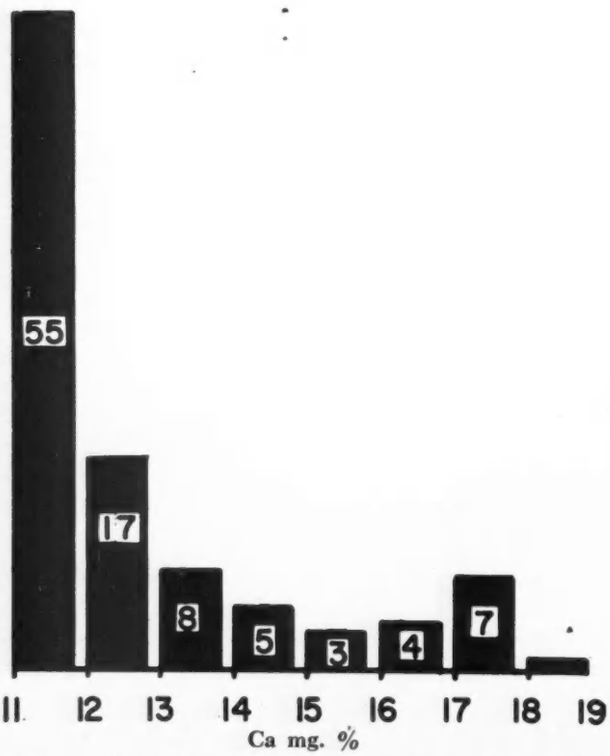

Fig. 1.—Presenting levels of serum calcium (100 patients).

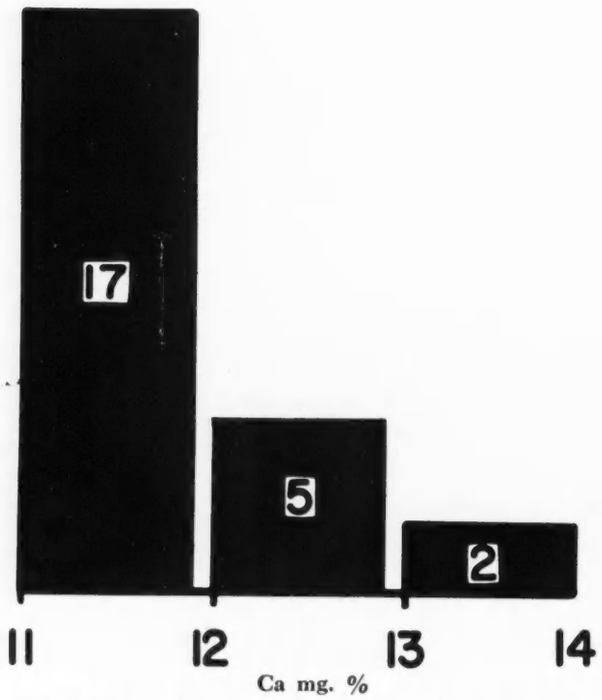

Fig. 2.—Presenting levels of serum calcium (24 patients without symptoms).

always a direct relationship between the degree of hypercalcemia and severity of symptoms. There is a marked variation from individual to individual in the ability to tolerate elevated blood calcium levels. It has been noted repeatedly in this study that a patient with only slightly elevated serum calcium may be in great distress, whereas another patient with values of 15 mg. %, or even higher, may be disturbed very little. In fact, an elevated serum calcium may produce no symptoms, as occurred in 20 of these 100 patients. Within this asymptomatic group, as shown in Fig. 2, serum calcium values up to 13.8 mg. % were observed.

Hypercalcemia, when giving rise to symptoms, expressed itself in one or more of four general ways (Table III).

(a) Seventy-five per cent of the symptoms recorded were referable to the gastrointestinal system; time and again, there was a history of anorexia, nausea, vomiting and constipation.

(b) Thirst, nocturia, polyuria and dry mouth reflected the underlying disturbances in water metabolism.

(c) Symptoms referable to the nervous system are of particular importance because they may lead the unwary to believe that intracranial metastatic disease is present. Within this group of symptoms drowsiness was most frequent. Several patients complained of blurring of vision, a symptom which, to the best of our knowledge, has not previously been ascribed to hypercalcemia. Double vision and difficulty with speech were interpreted as an expression of profound muscular weakness, rather than as a manifestation of focal disease.

TABLE III.—SYMPTOMS ASSOCIATED WITH HYPERCALCEMIA

Nausea	46	
Vomiting	40	
Anorexia	28	
Constipation	28	74%
Abdominal discomfort	3	
Diarrhea	1	
Dysphagia	1	
Thirst	7	
Nocturia	7	11%
Polyuria	6	
Dry mouth	3	
Drowsiness	8	
Blurred vision	3	
Dizziness	2	
Diplopia	1	
Dysarthria	1	
Lightheadedness	1	10%
Paresthesiae	1	
Restlessness	1	
Depression	1	
Confusion	1	
Weakness	6	
Malaise	4	5%
Fatigue	4	

(d) Finally, the symptoms of weakness, malaise and fatigue were attributed to hypercalcemia rather than underlying disease, at least in some cases, because these symptoms disappeared with the correction of the hypercalcemia.

In considering the signs of hypercalcemia it is important to note (Table IV) that those indicating disturbance of cerebrocortical function are the most frequent. The significance of lethargy, drowsiness and stupor must be recognized and lead to correction of the underlying disturbance; otherwise a progression to coma and death is almost inevitable. The general atonia which Collip[1] described in his animals is also to be observed in human patients in the form of muscle weakness with diminished or absent reflexes.

The serum phosphorus levels in these patients is of interest, but usually not of practical importance in the management of the individual case. We found, as have others, that the serum phosphorus most often was within normal range, but occasionally was either elevated or low. High levels were associated with renal failure.

TABLE IV.—SIGNS ASSOCIATED WITH HYPERCALCEMIA

Lethargy, Drowsiness, Stupor	18	
Disorientation	7	
Apprehension	3	
Confusion	2	
Inattention	1	50%
Incoherence	1	
Confabulation	1	
Depression	1	
Behaviour problem	1	
Incontinence	1	
Muscle weakness	6	
Absent reflexes	5	
Diminished reflexes	4	
Dysarthria	3	
Slowness of movement	2	35%
Miosis	1	
Diplopia	1	
Dysphagia	1	
Babinski response	1	
Urinary retention	1	
Dehydration	9	
Cliguria	2	15%

In five of our patients, one with acute leukemia, one with lung cancer, one with myeloma and two with breast cancer, low phosphorus levels were observed. The patient with lung cancer in this group, and three other patients observed by us in the previously mentioned study, one with lung and two with cancer of the tongue, had no evidence of bone involvement. They were of the type who had some of the biochemical features of hyperparathyroidism described by others.[19, 20] In none of this group with low phosphorus levels was surgical removal or total destruction of tumour by radiation possible.

About one-half of our patients had an elevated blood urea, and several points are to be emphasized in this regard. Hypercalcemia precedes the elevation of blood urea and where the blood urea initially is normal, it usually will rise as hypercalcemia continues or becomes more marked. This lag in the onset of renal failure has its counterpart in the delayed return of renal function to normal following correction of the hypercalcemia. It may take two or three weeks for the blood urea to return to normal in such cases.

Our experience suggests that, with the hypercalcemia of malignant disease, it is unusual for the constitutional features of uremia to appear unless the kidneys have been affected by some other disease process. In only seven of our cases did the blood urea rise above 100 mg. %, and in each of these a complicating factor was present. In one patient the kidneys showed marked leukemic infiltration, and in another patient the nephropathy of myelomatosis was present. Two patients had hydronephrosis secondary to ureteral obstruction by tumour. Acute nephritis and pyelonephritis were complicating factors in two other patients and the seventh patient had severe hypervitaminosis D.

From a practical standpoint, the management of hypercalcemia in malignant disease is based on three principles: removal of precipitating factors, restoration of fluid balance and treatment of the underlying disease. We have had little experience with the use of chelating agents. In 33 cases the management of hypercalcemia was not undertaken because of its relative unimportance in the total problem, or because the patient was in the terminal phase of his illness. In the remainder, specific steps were taken to correct the hypercalcemia.

In the milder cases, the control of vomiting and restoration of adequate fluid intake were sufficient measures. In the more severe cases intravenous fluids were necessary. In patients suffering from multiple myeloma, lymphoma and leukemia appropriate chemotherapy was used to control the underlying disease. The majority of our patients had breast cancer and where hypercalcemia had been

induced by treatment it was discontinued or altered. However, in many of these patients the problem was sufficiently serious to require the use of agents such as hydrocortisone and prednisone in addition. At least 3000 c.c. of intravenous fluids daily and 100 mg. of hydrocortisone in each litre of fluid were given. When vomiting ceases, the patient is placed on prednisone 20 to 30 mg. daily by mouth and is encouraged to drink large amounts of fluids, and then when the patient's condition improves sufficiently, the prednisone is gradually withdrawn.

With these measures, calcium values returned to normal levels in half the patients treated and remissions of as long as 18 months were obtained. Most of these patients were able to return to a comfortable and useful life.

The following patient suffering from breast cancer (Fig. 3) illustrates some of the factors which may alter the rate of tumour growth and also rapidly influence the serum calcium level.

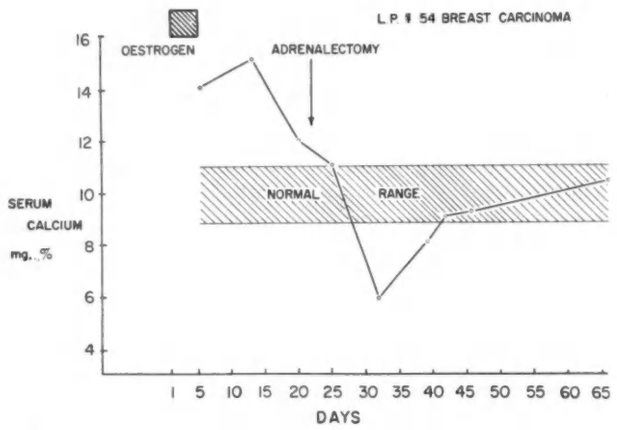

Fig. 3.—An illustration of the effect of hormonal changes on serum calcium values in a patient with breast cancer and bone metastases.

L.P., a 54-year-old woman with breast cancer, was first seen in 1947, at the age of 44 years, with a duct carcinoma of the breast. Simple mastectomy and oophorectomy were performed. She was well for eight years, but in 1955 developed nodules on the chest wall which were treated by radiation. In the summer of 1956 she complained of back pain, and when radiographs showed only generalized demineralization, she was given a spinal support. Her back pain became worse, and in February 1957 radiographs showed increased demineralization with definite metastases in the right sacroiliac area. On March 1, 1957, she was placed on stilbestrol 5 mg. daily, but five days later she felt increasingly ill. Her back pain was worse and she developed nausea and frequency of urination. Because serum calcium on the following day was 14 mg. %, stilbestrol was discontinued. On March 13 the serum calcium was 14.8 mg. %, phosphorus 5.3 mg. %, and blood urea nitrogen 48 mg. %. By March 15 she was feeling better and on March 20 her serum calcium was 12 mg. %, but, meanwhile, partial spinal cord compression had occurred. On March 25 her serum calcium was 11 mg. %, phosphorus 2.7 mg. % and urea nitrogen 14 mg. %.

It was assumed that the growth of the tumour had been accelerated by estrogen therapy, and on March 27 adrenalectomy was performed to obtain further estrogen deprivation. Five days after operation the patient felt "numb all over" and showed the classical signs of hypocalcemia. Her serum calcium at this time was 5.8 mg. %. Calcium gluconate intravenously, calcium lactate orally and vitamin D were given to control the symptoms of hypocalcemia, but the serum calcium did not return to normal levels for about two weeks. Presumably, the estrogen deprivation which followed adrenalectomy so profoundly inhibited tumour growth that calcium was laid down rapidly in bone previously involved by tumour, leaving insufficient quantities to maintain normal serum calcium values. This explanation is probably correct because radiographs taken one month and three months later showed multiple areas of dense calcium deposition. The patient remained in remission for two years after adrenalectomy.

DISCUSSION

The main purpose of this report is to emphasize the relatively high incidence of hypercalcemia which accompanies malignant disease. The condition makes its appearance insidiously and there may be no symptoms betraying its presence or no radiological evidence of involvement of bone. In our own experience the majority of patients with hypercalcemia and malignancy have breast cancer. Others[21,24] have reported a similarly high incidence of hypercalcemia in this type of cancer.

The occurrence of hypercalcemia in association with breast cancer raises several points for discussion. In about half of this group of patients the hypercalcemia occurred spontaneously. Only nine of the 65 patients with breast cancer had been on androgen therapy. Indeed, androgen was not believed to have had a special effect because all of the other accepted forms of therapy for breast cancer were associated with hypercalcemia as well. A patient may come into hospital with a normal serum calcium, receive radiation therapy and then within a few days develop hypercalcemia. A possible explanation of this interesting event is that such treatment may cause nausea and thereby interfere with adequate fluid intake, but it is important that symptoms such as nausea be recognized as evidence of hypercalcemia, and not interpreted as a manifestation of radiation sickness.

In his excellent papers, Myers[21, 23, 24] has stressed the neurological features as predominant in this clinical syndrome. It has been our experience that hypercalcemia usually expresses itself initially in symptoms referable to the gastrointestinal tract. The occurrence of nausea, anorexia, vomiting and constipation should always arouse suspicion of hypercalcemia. Drowsiness, lethargy, stupor or other manifestations of disturbances within the central nervous system may not appear until further elevation of the serum calcium has occurred. Blurring of vision, as a symptom of hypercalcemia, has not been mentioned previously by other authors, to the best of our knowledge. Diplopia,

dysphagia and similar symptoms may be ascribed to generalized muscle weakness and are not interpreted by us as indicating the presence of focal lesions within the central nervous system.

The effects of hypercalcemia on the electrocardiogram are of particular interest. Hoff, Smith and Winkler[25] have shown in animals that infusion of calcium salts will produce an initial effect comparable to vagal stimulation with bradycardia, prolonged A-V and intraventricular conduction. With serum calcium levels higher than ever occur in the human, a ventricular excitatory phase supervenes, which is characterized by frequent ventricular extrasystoles, ventricular tachycardia and eventually ventricular fibrillation with death. In the human there is evidence of a comparable vagal effect when calcium is infused.[26] To our knowledge no regular or distinct pattern of change in the electrocardiogram has been described when hypercalcemia occurs in humans as a manifestation of disease.[27] Our experience is similar to that of Gerbrandy and Hellendoorn,[22] in that we have not observed any changes in the electrocardiogram which might be considered characteristic of hypercalcemia. Also, in the presence of marked hypercalcemia, interpreting an electrocardiogram is more difficult because of the associated renal failure.

Hypercalcemia of even moderate degree may occur without symptoms or signs, and there is a significant difference in the ability of individuals to tolerate elevated levels of serum calcium. Some of our patients, who developed symptoms of hypercalcemia with serum calcium values of 10.5 mg. % were noted previously to have calcium values in the lower limits of normal, and the question is raised whether figures in the upper limits of normal are, in fact, "hypercalcemia" for this particular group. It would be helpful, especially in breast cancer, to obtain the normal serum calcium value of each patient as a base line for future comparison.

Five patients had low serum phosphorus with high serum calcium, but because the removal of the primary tumour was not possible in them we do not know if they are similar to those described by Connor, Thomas and Howard[19] and Plimpton and Gellhorn[20] in whom removal of the tumour was followed by return of serum calcium and phosphorus to normal levels. It is not known whether such tumours produce a substance similar to parathormone, but parathyroidectomy has been performed on patients with hypercalcemia and malignant disease, with beneficial results.[28]

We wish to draw attention again to the observations concerning altered renal function in association with hypercalcemia for the serum calcium and blood urea do not rise simultaneously. There is a lag in the rise of blood urea and a corresponding delay in its fall after correction of hypercalcemia. Gerbrandy and Hellendoorn[22] demonstrated the same phenomenon in terms of creatinine clearance and considered that the failure of renal function was due to calcium deposition and degenerative changes in the renal tubular cells. The clinical features of uremia appear in this group of patients only when other kidney disease is present, in addition, and this is of interest from both the academic and practical standpoints. For example, it is important to recognize that, when the blood urea goes to very high levels, another type of renal disease is probably present which may respond to specific treatment.

The clinical course of a patient with hypercalcemia, uncomplicated by other kidney disease, who has deteriorated to the point of death can be differentiated clearly from that of the patient with uremia. Generally in the former group of patients one does not see the neuromuscular excitability, the manifestations of acidosis, the severe anemia and other features usually associated with death in uremia.

SUMMARY

The clinical features of 100 patients with hypercalcemia and malignant disease are described.

Nausea, vomiting, anorexia and constipation account for 75% of all symptoms.

The most common signs of hypercalcemia are those associated with disturbances of cerebrocortical function and include lethargy, drowsiness and stupor.

Two-thirds of the patients had breast cancer.

More than half of the patients with breast cancer were receiving no treatment for their disease when hypercalcemia was first observed. In the remainder hypercalcemia followed or was associated with all of the accepted forms of treatment of metastatic disease.

Simple measures may correct hypercalcemia and prolong useful life in a significant number of patients.

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PRURITUS OF PREGNANCY A SYMPTOM OF HEPATIC DYSFUNCTION, WITH A REPORT OF TWO CASES*

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A FORM of jaundice occurring in the latter part of pregnancy, unrelieved until delivery and tending to recur in subsequent pregnancies was described as early as 1907.[1] The clinical picture, course and prognosis of this jaundice differs from that caused by eclampsia and from conditions unrelated to pregnancy such as infectious hepatitis, hemolytic jaundice or cholelithiasis. It has been called idiopathic or recurrent jaundice of pregnancy.

Pruritus gravidarum has also been recognized for many years, but it has been appreciated by only a few authors that these two conditions are manifestations of the same disorder. Most case reports concerning this syndrome come from Scandinavia, and neither the concept of recurrent jaundice nor pruritus associated with pregnancy is well known on this continent. Sherlock makes no reference to either in the first edition of her text on diseases of the liver and biliary system in 1955[2] but devotes one paragraph to this subject in the second edition.[3] The purpose of this article is to present a report of two cases in which pruritus was the chief feature and to review briefly the literature on this subject.

CASE 1.—Mrs. P.R., 26 years old, had her last normal menstrual period on September 8, 1959. During the first trimester she suffered from moderately severe nausea and vomiting. On March 22, 1960, she reported itchiness of the arms and legs. This became progressively worse, was associated with occasional nausea and vomiting, and interfered with her sleep. She did not notice jaundice, pale stools or dark urine. Her only previous pregnancy resulted in a spontaneous abortion at three months and was accompanied by slight nausea and vomiting but no jaundice or pruritus; otherwise her past history was quite unremarkable. There was no family history of jaundice or pruritus associated with pregnancy.

She was admitted to the Toronto East General Hospital for investigation of the pruritus on April 26, 1960. On examination she was at about the 32nd week of her pregnancy and appeared healthy, although she was in moderate distress from generalized pruritus. Excoriations were present on the skin in various areas, but there was no jaundice. The general physical examination was within normal limits. The liver was not enlarged. Laboratory tests revealed the following: a hemoglobin of 75% (11.4 g.), a leukocyte count of 9100 per c.mm. with a differential of neutrophils 67%, stab forms 5%, monocytes 6%, eosinophils 2%, lymphocytes 20%. The urinalysis was negative for sugar, albumin, urobilin, microscopic examination, but positive for bile. The serum bilirubin was 1.0 mg. %, the serum alkaline phosphatase was 33 units (King-Armstrong; normal 3 to 13 units), and the bromsulphalein excretion test showed 30% dye present after 35 minutes. The prothrombin time was 14 sec., control 12 sec. and electrophoresis of serum proteins showed: total proteins, 6.4 g. %; albumin, 3.2 g. %; alpha-1 globulins 0.32 g. %, alpha-2 globulins 0.81 g. %; beta globulins 1.40 g. %; gamma globulins 0.66 g. % (normal beta globulin 0.70-0.89 g. %).

The patient was treated with antihistamines, sedatives and local applications to the skin, without benefit. The pruritus became progressively worse although the alkaline phosphatase did not exceed 35 units and the highest recorded serum bilirubin was 1.5 mg. %.

The patient went into labour in a normal manner and delivered a healthy female infant on May 25, 1960, 24 days before her expected date of confinement. Following delivery the pruritus improved immediately and was completely relieved by the time she left hospital one week later. Her alkaline phosphatase level on May 31 was 23 units and was not determined again until March 30, 1961, when it was 8.4 units. On May 31 the serum bilirubin was 0.4 mg. %; bromsulphalein excretion test showed that no dye was present after 35 minutes; serum electrophoresis gave values of, total proteins 7.5 g. %; albumin 3.24 g. %; alpha-1 globulin 0.29 g. %; alpha-2 globulin 1.43 g. %; beta globulin 1.62 g. %; gamma globulin 0.91 g. % (normal beta globulin 0.82-1.05 g. %). The serum proteins were analyzed again several months later, at which time they were entirely normal.

CASE 2.—Mrs. V.N., 27 years old, had her last menstrual period on June 16, 1960. In the first trimester she suffered from moderately severe nausea and vomiting and about October 1960 became aware of pruritus. This became progressively worse and she noticed that it was particularly bad during the 12 hours after ingestion of alcohol. The pruritus was not associated with nausea, vomiting, jaundice, pale stools or dark urine. The patient had two previous pregnancies each associated with progressively severe pruritus in the last trimester. In the first pregnancy the pruritus disappeared overnight after delivery and in the second pregnancy it was gone at the end of the first week postpartum. Otherwise, her past history was unremarkable and there was no family history of similar disturbances.

This woman was admitted to the Toronto East General Hospital for investigation of the pruritus on January 8, 1961. On examination she was at about the 28th week of new pregnancy and appeared healthy. Otherwise general physical examination was quite unremarkable. Laboratory investigation established the following results: the hemoglobin was 71% (10.8 g.); the leukocytes numbered 17,400 per c.mm. with a differential count of neutrophils 90% and lymphocytes 10%. The urinalysis was slightly positive for bile and negative for urobilin. The serum alkaline phosphatase level varied between 46 and 62 units (King-Armstrong). The serum bilirubin was 0.4 mg. %, serum cholesterol was 215 mg. %, thymol turbidity was 2.5 units and the cephalin-cholesterol flocculation test was negative. The bromsulphalein excretion test was done and 35% of the dye was present after 35 minutes. The prothrombin time was 13 sec., control 15 sec. and

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the serum glutamic oxaloacetic transaminase level was 4 units; the serum electrophoresis determination gave values of total proteins 6.4 g. %; albumin 2.5 g. %; alpha-1 globulin 0.58 g. %; alpha-2 globulin 1.02 g. %; beta globulin 1.47 g. %; gamma globulin 0.77 g. % (normal beta globulin 0.70-0.89 g. %).

The patient was treated with antihistamines, sedation and local treatment to the skin without benefit. The pruritus gradually became more severe and interfered with her sleep. Her serum alkaline phosphatase level remained about 60 units and the serum bilirubin did not rise above 1.01 mg. %.

On February 21, 1961, after a normal labour she delivered normal twins, a boy and a girl. Her expected date of confinement had been March 23. The pruritus improved immediately after delivery and was completely gone within two weeks. A follow-up determination of alkaline phosphatase on April 17 was 9.6 units and a repeat paper electrophoretic analysis of the serum proteins was entirely normal on the same date.

COMMENTS

These two cases are undoubtedly examples of what was formerly called pruritus gravidarum. Eastman states that itchiness sometimes gives rise to intense suffering and can seriously impair the general condition of the patient. In the tenth edition of his textbook he states that termination of the pregnancy is sometimes justified for this reason, but this statement is not repeated in later editions.[4, 5] He does not relate the pruritus to involvement of the liver in any way. Kasdon[6] reported 35 patients with pruritus in a series of 365 pregnancies, an incidence of 13%. The itchiness in these cases was more marked on the abdominal wall and worse during the last trimester. He did not describe associated jaundice and tests of liver function were not done. The increased alkaline phosphatase, abnormal bromsulphalein excretion and slightly raised serum bilirubin in our cases would seem to indicate that these are examples of the same disorder which is responsible for the so-called recurrent jaundice of pregnancy. Although described in 1907,[1] very little mention of this syndrome can be found in the literature until 1954 when Svanborg[7] described seven cases characterized by severe pruritus and mild jaundice in the last trimester of pregnancy.

The condition was not investigated thoroughly until Thorling[8] published his excellent monograph "Jaundice in Pregnancy" in 1955. This author described 38 patients with jaundice, 35 of whom had associated pruritus which usually preceded the jaundice by several weeks. Seventy per cent of his patients showed a tendency toward recurrence in subsequent pregnancies, and in 50% of the cases with a recurrence, pruritus was present without jaundice. Symptoms usually subsided within a week after delivery. The serum alkaline phosphatase was between 20 and 35 units in most cases although in one it was 140 (Buch and Buch method: normal 1-8 units). The serum bilirubin varied between 1.3 and 9.2 mg. %. Thymol turbidity and cephalin-cholesterol flocculation tests were usually normal and the prothrombin time was slightly prolonged in three cases. Bromsulphalein excretion tests were not done. The average length of gestation was 38.4 weeks as compared to 41.5 weeks in the normal patient.

In 1959 Svanborg and Ohlsson[9] reported an additional 22 patients with recurrent jaundice of pregnancy.[7] Seventeen had severe pruritus, and laboratory investigation yielded results similar to Thorling's cases. Liver biopsies were performed in five cases and the histological appearance was similar in all. The chief feature was accumulation of bile pigment in the bile capillaries, some of which were greatly dilated. These changes were more frequent about the central vein than in the portal areas. Degenerative changes in liver cells were inconstant and minimal and were considered to be secondary to the bile stasis. There was no necrosis of liver cells and no inflammatory reaction. In two cases the liver biopsy was repeated after delivery and in both a completely normal histological structure was seen.

Jefferies and Sleisenger[10] classified this condition with disorders grouped under the term intrahepatic cholestasis and included certain cases of viral hepatitis and hypersensitivity reactions to drugs such as chlorpromazine and thiouracil. Intrahepatic cholestasis without structurally demonstrable obstruction anywhere in the biliary tree has been discussed most thoroughly by Popper, Schaffner and Szanto.[11, 12] Although the pathogenesis remains obscure, it has been suggested that the bile is altered in some way, becoming more viscid or inspissated. In our opinion the term intrahepatic cholestasis is better than cholestatic jaundice, for it allows inclusion of those cases characterized by pruritus alone as well as those with jaundice.

The two cases described in this report differ from most of those previously reported in that severe pruritus was present without jaundice. In the second patient, pruritus was present during each of three pregnancies without jaundice, and it has been well recognized that both of these symptoms tend to recur with subsequent pregnancies. The evidence of disturbed hepatic function in our patients consists of elevated serum alkaline phosphatase levels and abnormal bromsulphalein excretion tests. Serum bilirubin levels were only very slightly raised. The elevation of beta globulins is not by itself indicative of abnormal liver function, for this finding has been observed in perfectly normal pregnancies.[13] In both cases the pruritus disappeared and the abnormal tests returned to normal promptly after delivery. Both patients had premature delivery, which was noted in other cases reported in the literature.

It is interesting to speculate on the cause of this disorder. It may be that the symptoms are due to an accentuation of a process that occurs in normal pregnancies. Although liver biopsy studies have demonstrated no characteristic histological changes in normal pregnancy,[14, 15] the serum alkaline phos-

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phatase level rises slightly. It averages 4 units (Buch and Buch method: normal 1-8 units) at the tenth week of pregnancy and remains at this level until the last trimester, when it gradually rises to an average of 10 units at the time of delivery.[8] A slight increase in serum bilirubin is also not unusual during the final month in normal pregnancy.[9] These changes are more pronounced in multiple pregnancies.[7] Abnormal bromsulphalein excretion has occasionally been demonstrated in the latter part of pregnancy.[16] It has been suggested that the increased intra-abdominal pressure in pregnancy causes interference with bile flow. However, this does not occur with other causes of increased intra-abdominal pressure. Moreover, in our patients there has been a selective failure to excrete alkaline phosphatase in the bile, not failure of bile excretion itself. These patients who have severe pruritus but only a slight increase in serum bilirubin cast doubt on the commonly accepted explanation of the pruritus in obstructive jaundice, i.e. the presence of bile salts in the skin. Patients with high alkaline phosphatase from other causes, e.g. Paget's disease of bone or secondary carcinoma of the liver, do not have pruritus. The actual cause of the pruritus remains obscure. It would appear to us that the abnormality of the liver function in these cases is of metabolic origin and is related to the presence of a fetus. In this sense it is a benign toxemia of pregnancy quite different from the hepatic necrosis that may accompany eclampsia.

SUMMARY

Two cases of severe pruritus associated with pregnancy and accompanied by elevated serum alkaline phosphatase and abnormal bromsulphalein excretion but without jaundice have been described. The literature has been summarized and the possible mechanisms have been discussed. Liver biopsies were not done, but these cases can best be grouped with those described elsewhere as intrahepatic cholestasis. Treatment is directed to the symptoms alone and the prognosis for both mother and infant is excellent.

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KANAMYCIN: A REVIEW AND REPORT OF CLINICAL EXPERIENCES WITH PR. VULGARIS INFECTIONS*

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ONE OF THE most difficult aspects of the assessment of the action of antibiotics lies in determining their clinical efficacy and deciding if the clinical response is due directly and entirely to the drug being evaluated.

This is particularly true when one is aware of the other numerous factors at work in an individual case such as the immunity of the host, the degree of suppuration, the adequacy of the circulation, the virulence of the organism, the presence of unrecognized mixed infection, the ability of the chosen drug to penetrate the various anatomical compartments, the presence of urinary tract obstruction and the influence of such factors as surgical drainage and proper dosage.

Many reports of the use of kanamycin have been published in the medical literature since it was first introduced for clinical use. Although its clinical application is limited, we feel that it is of value in certain infections in spite of its high toxicity. Before reporting the results in five cases treated with kanamycin, a short review of its bacterial spectrum, toxicity and dosage, will be presented. In many respects, this antibiotic is similar to neomycin and streptomycin.

Bacterial Spectrum

Kanamycin is bactericidal in action, and in general its bacteriological spectrum is very similar to that of neomycin.[1] It is not a suitable agent for the treatment of streptococcal or pneumococcal infection. Against staphylococci, its efficacy is accepted. It has a wide range of action against Gram-negative organisms, including many strains of *Pr. vulgaris*, *E. coli*, *A. aerogenes*, Salmonella and *K. pneumoniae*.[2] Hence, clinically, kanamycin appears to have its greatest usefulness in treating stubborn Gram-negative infections and, to a lesser degree, general staphylococcal infections resistant to other antibiotics. In genitourinary tuberculosis, kanamycin is as effective as streptomycin;[3] however, because of its greater nephrotoxicity, it probably should be used only against tubercle bacilli highly resistant to streptomycin. Some degree of cross-resistance is known to exist between kanamycin and streptomycin.[4]

Toxicity.—The usefulness of kanamycin, when given parenterally, is limited by its toxicity and therefore it should be reserved for serious infections with organisms resistant to less toxic antibiotics. Aside from slight local irritation and occasional eosinophilia, the major toxic manifestations are renal and otic. Although cylindruria, albuminuria and changes in specific gravity may occur with kanamycin and persist throughout treatment, they cannot be depended upon to reveal early nephrotoxicity.[5] This was suggested in one series of cases in which the renal clearance studies showed an appreciable decrease in 47 to 52% of cases, whereas proteinuria, specific gravity and phenolsulfonphthalein (P.S.P.) studies showed changes in only 10 to 37% of the cases studied.[6] In general, renal toxicity with kanamycin is less than with neomycin[7] and, as indicated above, its toxicity is greater than that of streptomycin. Kanamycin should not be given to any patient who has the slightest evidence of pre-existing renal damage.

Although total dosage and length of therapy are of considerable importance in ototoxicity, the decisive factor appears to be the presence of impairment of renal excretion. Lecca *et al.*[8] reported three cases of progressive permanent deafness in patients receiving as little as 14 g. of kanamycin, and all three patients had elevated blood urea nitrogen, ranging from 45-86 mg. %.[8] Vestibular toxicity with kanamycin is less than that with streptomycin, and cochlear toxicity with kanamycin is less than that with dihydrostreptomycin.[7]

Dosage.—The dose of kanamycin should be estimated on a basis of bodyweight of 15 mg. per kg. per day.[5] For systemic use it is administered by the intramuscular or intravenous route; in the latter case, in the form of a solution containing 0.5 to 1.0 g. diluted in 10 to 25 ml. of 5% glucose in normal saline and given over a three-minute period, or as 0.5 to 1.0 g. diluted in 200-500 ml. and given at a rate of 60 drops per minute. The intramuscular route is recommended except for patients with extremely severe infections, when it may be necessary to give the drug intravenously in spite of the risk of greater toxicity. The dosage may be further altered if the organism is highly sensitive.[9] Bunn, Baltch and Krajnyak[9] consider that it is non-toxic in the presence of normal kidney function, when given in doses of 1.5 to 2.0 g. daily and in a total amount of less than 40 g.[9] However, in the presence of depressed kidney function, the dosage must be smaller or preferably it should not be used at all owing to the risk of eighth nerve damage as well as that of further renal impairment.

When given orally, kanamycin has proved to be one of the most effective single agents available for intestinal antisepsis since it is poorly absorbed.[10] The average oral dosage is 1 g. every six hours. After a total dose of 4 g., an average blood level of 4 μg. may be attained in eight hours. Contrary to previous statements, oral administration may result in toxic systemic blood levels, particularly in patients with severe impairment of renal function or in patients with any inflammatory process in the

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gastrointestinal tract. When kanamycin is used in the treatment of hepatic coma, as an inhibitor of urea-splitting organisms, it should be remembered that such patients frequently have oliguria and azotemia and thus are more prone to toxic effects.[11] Last and Sherlock[12] further state that, under these circumstances, increased absorption may occur through a damaged gastrointestinal mucosa.

Kanamycin has been used intraperitoneally in conjunction with surgical procedures and with systemic broad-spectrum antibiotics in the successful treatment of 18 patients with established peritonitis.[13] The drug was placed directly into the peritoneal cavity in a dose of 0.5 g. diluted in 20 c.c. of sterile water. The infection was controlled, morbidity was decreased and all patients recovered without complications. However, it was suggested that the intraperitoneal administration of kanamycin or neomycin may be a major contributing factor in the production of cardiac arrest, or in respiratory depression when used simultaneously with anesthesia.[13] Moreover, fatal renal tubular necrosis has followed intraperitoneal instillation of 3 g. of neomycin after 36 hours; and in these circumstances, it must be assumed that a similar risk exists with kanamycin.

Bacteriology.—*Pr. vulgaris* was isolated in all five cases described in this report, and sensitivities were performed according to the standard Department of Veterans Affairs disc method, using 5 and 30 μg. Baltimore Biological Laboratories (BBL) discs against kanamycin, neomycin and streptomycin. Table I summarizes these data, as well as giving the source of the infecting organism and the disease entity. These five strains were all sensitive to kanamycin.

CASE 1.—The first patient, a 23-year-old man, presented with a bilateral purulent hemorrhagic otitis media complicating an attack of influenza. He was acutely ill on admission with a temperature of 104° F., bilateral inflamed ear drums and a bloody purulent discharge from both external auditory canals, from which *Pr. vulgaris* was cultured. There were dullness and fine crepitations at the base of the left lung. Radiographic examination of the chest revealed a pneumonitis, but sputum cultures were negative. Antibiotic therapy included one day's treatment with chloramphenicol, to which the organism was reported later to be resistant. Erythromycin was started one day prior to kanamycin therapy and was given throughout the course of treatment; however, its effect can probably be discounted owing to the high incidence of resistance of *Pr. vulgaris* to this drug. Kanamycin was given in a dosage of 0.5 g. twice daily for six days. The temperature fell to normal within 24 hours of the institution of kanamycin therapy, and the discharging ears were completely dry in six days. The sedimentation rate decreased from 85 to 43 mm./hr. during the treatment. Supplementary topical therapy included a solution containing dihydrostreptomycin 2.5 mg. per ml., to which the organism was sensitive. A follow-up examination one month later showed no evidence of disease.

TABLE I.

Case No.	*Organism*	*Diagnosis*	*Source*	*Sensitivity* *Kanamycin*	*Neomycin*	*Streptomycin*	*Result*
1	*Pr. vulgaris*	Acute otitis	Ear	S	S	S	Cure
2	*Pr. vulgaris*	Fever, following a cystourethrogram	Urine	S	S	R	Cure
3	*Pr. vulgaris*	Cystitis	Urine	S	MR	R	Replaced by *E. coli*
4	*Pr. vulgaris*	Cystitis, following a nephrectomy for renal carcinoma	Urine	S	S	S	Cure
5	*Pr. vulgaris*	Following a prostatectomy	Wound	S	S	S	Cure

Blood and tissue levels.—Following an intramuscular dose of 0.5 g. of kanamycin, peak blood levels are reached in one hour, in the range of 25 to 30 μg./c.c.; then there is a gradual falling off in five to six hours, but blood levels of 0.9 μg/.c.c. may still persist after 12 hours.[14] Good therapeutic levels are present in the liver, muscles, lungs and kidneys. Much lower concentrations are found in the central nervous system, bone and bile.[7, 15] Kanamycin crosses the pleural and peritoneal membranes poorly. Urinary concentrations are high; 80% of the administered dose may be recovered from the urine during the first 24 hours.

Assessment of cases studied.—The criteria for judging clinical response in our series include the following seven points: (1) a decline of elevated body temperature; (2) a fall in sedimentation rate; (3) an improvement in the numbers and differential distribution of the leukocytes; (4) an improvement in the character of sputum or exudate; (5) a reversion of the culture to negative; (6) improvement of radiographic findings; (7) an amelioration in the overall clinical picture.

CASE 2.—This 20-year-old coloured man was admitted for investigation of severe hypertension which revealed a congenital, aplastic kidney on the right side and a hypotonic bladder. Following a cystometrogram, he developed fever, chills, pyuria and bacilluria. Urine cultures grew a spreading *Pr. vulgaris* sensitive to neomycin and kanamycin but moderately resistant to chloramphenicol. He was given a course of treatment with kanamycin 500 mg. intramuscularly every six hours for six doses, then 500 mg. every eight hours for five days. The blood urea nitrogen was normal before and after therapy. The temperature dropped from 102° F. to a normal level after two days and the sedimentation rate decreased from 78 mm./hr. to 43 mm./hr. on the third

day and to normal at the end of treatment. Urine cultures on the third day still grew *Pr. vulgaris* but the culture taken on the sixth day after institution of kanamycin therapy was sterile. A follow-up culture two weeks later showed no growth.

CASE 3.—A 74-year-old man with previously recognized chronic bronchitis with emphysema was admitted with acute respiratory infection which was treated with chloramphenicol; sputum cultures were negative. Subsequently, he developed symptoms of a urinary tract infection and the urine culture grew a *Pr. vulgaris*, sensitive to kanamycin but resistant to chloramphenicol. Kanamycin therapy was instituted in a dosage of 500 mg. every six hours intramuscularly for five days. There was satisfactory clinical improvement, and a urine culture four days after therapy was instituted was negative for *Pr. vulgaris* but showed a light growth of *E. coli*. It is of interest that before the institution of kanamycin therapy, a residual urine of 350 c.c. was obtained but thereafter catheter drainage was not necessary.

CASE 4.—A right nephrectomy was performed on a 55-year-old man, for hypernephroma. At the time of operation, frank pus was present in the pelvis of the diseased kidney. A culture from this exudate grew *Pr. vulgaris*. Urine cultures on the second and third postoperative days grew the same organism. He was given short courses of tetracycline and novobiocin before sensitivity tests showed that the organism was resistant to both of these drugs but sensitive to kanamycin. The latter was then administered in the dosage of 0.5 g. every eight hours for five days. On the third day of therapy, urine cultures became negative and remained so during further follow-up examinations. Coincident with reversion to negative urinary cultures, the patient had prompt clinical improvement.

CASE 5.—A 60-year-old man was admitted for a prostatectomy for adenocarcinoma of the prostate. Following radical perineal prostatectomy, he developed an extensive wound infection caused by *Pr. vulgaris* and a urinary tract infection due to *A. aerogenes*. The *Pr. vulgaris* was sensitive to kanamycin, but the sensitivity of the *A. aerogenes* to kanamycin was not determined. Kanamycin was given intramuscularly in a dosage of 250 mg. every six hours for three days and was then increased to 500 mg. intramuscularly every six hours for the next four days. Five days after the institution of kanamycin therapy, both urine and wound cultures were negative. There was a prompt decrease in the exudate from the wound and pyuria subsided. It is of interest that an eight-day course of sulfamethiozole (Thiosulfil) therapy prior to prostatectomy had had no effect on the urinary tract infection.

ANALYSIS OF RESULTS OF TREATED CASES

Clinical improvement was obtained in all of the five cases reported here in which the infecting organism was *Pr. vulgaris*. All of the *Pr. vulgaris* were reported by the laboratory to be sensitive to kanamycin. It is not known that this effect was due entirely to the administered kanamycin in all cases because of the simultaneous administration of another antibiotic and the use of other complementary therapy. In the urinary tract infections in one instance, replacement by another organism occurred. These case reports demonstrate that kanamycin in the dosage used caused no apparent otic or renal toxicity.

SUMMARY

Kanamycin in the dosage used and in short-term therapy had no toxic effects in the five cases studied.

Its usage is limited, but it has a place in the treatment of *Pr. vulgaris* infections.

The difficulty of assessing the clinical value of an antibiotic is stressed.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

THE SURGICAL TREATMENT OF GALL-STONE DISEASE

The danger of re-formation of gall-stones after cholecystostomy is exceedingly small. In our series we observed but three cases in which stones had re-formed in the gall-bladder, and it is probable that in the majority of cases of supposed re-formation of gall-stones, the stones had not re-formed, but were incompletely removed at the primary operation; an accident which does not often happen when the operation is done early.

The function of the gall-bladder is to take the tension from the common and hepatic ducts and the ducts of the pancreas. It also acts to produce mucus, which protective substance, when mixed with the bile, tends still further to reduce the chances of pancreatic and other complications. The hypothesis that the function of the gall-bladder is that of bile storage is obviously erroneous, since there are from thirty to fifty ounces of bile secreted each day, and the capacity of the normal gall-bladder is but one ounce; a quantity relatively too small to be of much importance. In addition, there is not sufficient muscular tissue in the gall-bladder to enable it to contract for the purpose of emptying its cavity as do organs of storage function, for example, the stomach and urinary bladder.—William J. Mayo (Rochester, Minn.), *Canad. M. A. J.*, 1: 866, 1911.

PEMPHIGUS AS IT AFFECTS THE EYE*

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THE PURPOSE of this paper is to attempt to clarify the classification of pemphigus as it affects the eye and to present seven patients with such involvement.

Pemphigus can be divided into two main classes, systemic pemphigus and ocular pemphigus.[1-4] Of these, systemic pemphigus usually has a fatal termination.[5]

SYSTEMIC PEMPHIGUS

In systemic pemphigus there is a deterioration of health during which there are usually periods of good health followed sooner or later by exacerbations of systemic illness. Systemic pemphigus is characterized by intra-epidermal bullae and acantholysis.[6] The eye involvement, when it accompanies the systemic form, goes on to varying degrees of severe ocular disability. This eye involvement does not differ from that of primary ocular pemphigus.

Systemic pemphigus has been divided into four main types,[7] acute pemphigus, chronic pemphigus or pemphigus vulgaris, pemphigus foliaceus and pemphigus vegetans. Of these only the acute and the vulgaris types are accompanied by eye involvement. Acute pemphigus begins with a sudden onset with fever and runs a rapid course. Numerous bullae appear on the skin and mucous membranes, which burst, leaving a red discharging surface. The typical ocular findings may include a severe conjunctivitis with chemosis and edema of the eyelids, but frequently the patient dies before the eye symptoms typical of pemphigus appear. The lesions of chronic systemic pemphigus or pemphigus vulgaris appear as bullae of the skin and mucous membranes without preceding erythema. The skin bullae dry, leaving erythematous scaly patches which ultimately disappear. The condition may go on for years, fresh crops appearing as others disappear, but accompanied by a gradual decline in health until death occurs. Pemphigus vulgaris is usually a disease of the later years, although it is occasionally found in younger persons. It should be differentiated from acne rosacea, erythema nodosum, psoriasis, erythema multiforme bullosa, dermatitis herpetiformis and epidermolysis bullosa.

Systemic pemphigus is treated with the corticosteroids in high dosage. The eye complications which are similar to those of ocular pemphigus are treated symptomatically.

OCULAR PEMPHIGUS

In ocular pemphigus no systemic disease is present although bullae of the mucous membranes of the nose and throat may be present, and skin lesions in about half of the cases.[2]

When pemphigus affects the eye, it has the following characteristics.[2, 8] A conjunctival eosinophilia may be present and the conjunctiva in the region of the lower fornix is edematous and becomes infiltrated with lymphocytes and plasma cells. Transient thin-walled bullae may be present but are seldom well formed, as their walls break down quickly, leaving greyish ulcerated areas. The subepithelial tissues are infiltrated with lymphocytes and plasma cells. A glary film of mucus develops in the lower fornix,[13] followed by a fibrinous exudation resulting in the development of a pseudomembrane or deeper membrane. Ulcerated areas on the bulbar and palpebral conjunctiva adhere together. Subepithelial connective tissue forms in excess and later contracts, resulting in vertical bands of adhesion at the sites of the ulcerated and adherent areas. With a further advance of the ulcerative process and contraction of the fibrous tissue, entropion, symblepharon, trichiasis and desiccation may develop.[9, 10] Aided by the trauma of exposure, desiccation and trichiasis, the corneal damage increases. There is also the inherent tendency of the disease to form vesicles and bullae in the cornea, which causes further damage. Desiccation produces changes in the osmotic tension of the cornea, which becomes edematous and separates from Bowman's membrane. A vascular pannus then invades the cornea between Bowman's membrane and the corneal epithelium; with advancement of the pannus the edema subsides. This vascular pannus eventually becomes devascularized, and the patient is left with an opaque cornea. At any stage of the process trichiasis may further damage the cornea and secondary infection may follow, causing deep ulceration or perforation.

The differentiation of ocular pemphigus from pemphigus vulgaris is chiefly through the absence of systemic disease in the former, but it should be distinguished from trachoma, caustic burns and Stevens-Johnson's syndrome.

The treatment of ocular pemphigus is unsatisfactory. An attempt should be made to prevent damage from desiccation, secondary infection and the formation of adhesions.

Secondary infection may be prevented by the use of sulfonamides and antibiotics. Occlusion of the lacrimal puncta has been advocated by Elliot[11] in selected cases to combat the desiccation. The use of artificial tears has been tried by Friedman and Wright,[10] and scleral contact lenses to prevent symblepharon have been suggested by Ridley.[12] A

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corneal graft has been employed to replace a damaged cornea with limited success by Thompson.[13] The severe lower fornix adhesions frequently encountered in this condition have been treated by Friedman and Wright[10] by deep dissection of scar tissue and the use of split-thickness mucous membrane transplants. However, whatever treatment is used, the process usually is progressive in a relentless manner.

CASE REPORTS

CASE 1.—H.G., a white man aged 61 years, was admitted to hospital on April 27, 1960, with hemoptysis, chronic ocular irritation and skin lesions. In 1926 the patient has been treated for pulmonary tuberculosis, and in 1949 he developed a sore throat with hoarseness but biopsy of the lesion was reported to be benign. In 1952 an investigation following an episode of hemoptysis was negative. In the autumn of 1958 the patient coughed 3 or 4 oz. of red blood, and in October 1959 some epistaxis was noticed, followed three to four weeks later by a sore throat, hoarseness of the voice and further hemoptysis. A small ulcer on a vocal cord was biopsied and reported as benign. Ulcerations also appeared on the umbilicus and in the rectum, where they caused bleeding. Similar ulcers developed on the skin of the face, where they formed a scab which fell off after a week or two, leaving a shallow ulcer. None of them healed completely. In the mouth the ulcerations were smaller, measuring about 5 mm., red, tender, with a white centre. In December 1960, the eyes became red, sensitive to light and chronically irritated, and these symptoms gradually became worse.

On examination three ulcers which were covered by a scab were found on the nose. They were shallow and surrounded by an indurated area of inflammation. Ulcers were also present on the scalp, and there were a few raised red areas on the face and scattered dull yellow plaques. Groups of ulcers present in the mouth were surrounded by raised red areas. The umbilicus contained some chronic serous discharge, and excoriations were present around the rectum.

The vision was 20/60 in the right eye and 20/40 in the left. Incipient blepharitis and entropion were noted, and both lower fornices were completely filled by adhesions, more marked in the right eye. Vertical symblepharons were present in upper and lower fornices. The ocular movements were limited by adhesions, and the remaining bulbar conjunctiva was edematous. There was a marked decrease in lacrimal secretion, the precorneal film was deficient and the corneae were rough and irregular. Scraping of the conjunctivae did not reveal the presence of inclusion bodies, increased eosinophilia or any lymphocytic infiltration. There was no eosinophilic leukocytosis. A biopsy of the conjunctiva showed a few polymorphonuclear leukocytes, lymphocytes and plasma cells in the subepithelial tissue; the small vascular channels were dilated (Fig. 1). Section of an ulcerated area revealed the presence of mild acute and chronic inflammation. The patient was treated with adrenocorticotrophic hormone and massive doses of corticosteroids, with some relief of the symptoms.

In June 1961, his general condition deteriorated and he developed diabetes and a chronic chest infection. Death occurred on June 3 from the complications of

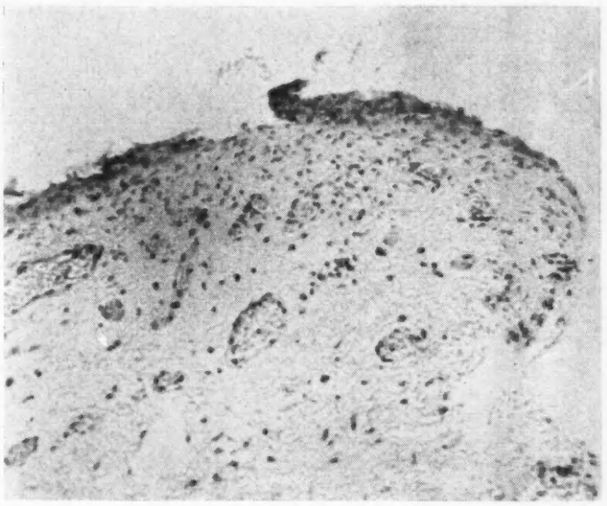

Fig. 1.—Case 1. The biopsy of the conjunctiva demonstrating a few polymorphonuclear leukocytes, lymphocytes and plasma cells in the subepithelial tissue. The small vascular channels are dilated (× 120).

massive steroid therapy, septicemia, renal failure, pyelonephritis, peptic ulceration and acute pneumonia. The autopsy did not confirm the diagnosis of pemphigus. However, a section of the skin of the umbilicus showed ulceration with exudation on the surface. At the edge of the ulcers there was a cleavage between the epidermis and dermis, a change which was in keeping with the clinical diagnosis of systemic pemphigus (Fig. 2).

CASE 2.—Mrs. M.S., aged 60 years, was first seen in July 1958 with a two-year history of chronic irritation of the eyes. Her vision was then 20/20 in each eye

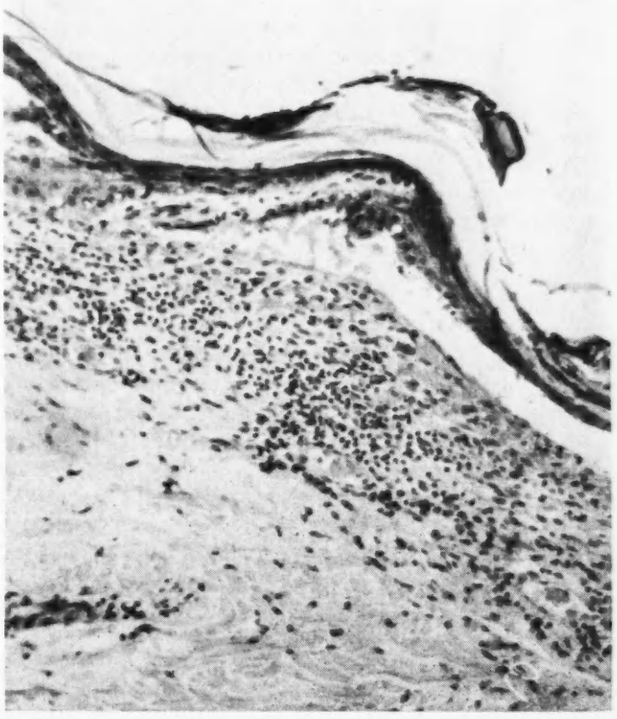

Fig. 2.—Case 1. A section of the skin of the umbilicus showing ulceration with exudation on the surface. At the edge of the ulcers there is a cleavage between the epiderm and dermis (× 120).

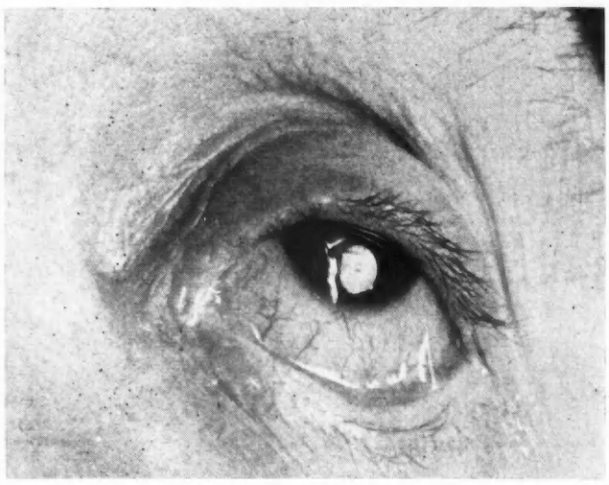

Fig. 3.—Case 2. Vertical symblepharon in the lower fornix of the left eye.

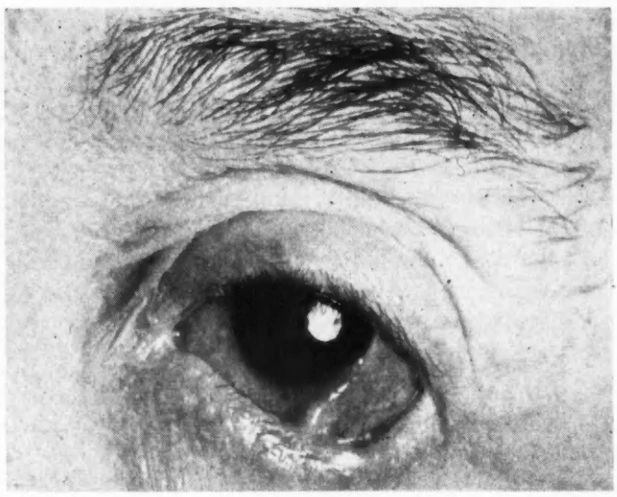

Fig. 4.—Case 2, five months postoperatively. The symblepharon has reformed in the left eye.

and she had some vertical symblepharons in both lower fornices. She was treated with local corticosteroids. One year later she was found to have cicatricial entropion in both eyes and trichiasis of the right lower lid. A dermatological consultation confirmed the diagnosis of pemphigus vulgaris, and she was treated for pemphigus of the soft palate, stomatitis, and chronic rhinitis with purulent discharge. She did not have an eosinophilic leukocytosis. In March 1960, the patient was admitted to hospital. Her vision was 20/40 in the right eye and she had light perception only in the left eye. There was entropion of both lower lids, and trichiasis of the right lower lid. Both lower fornices showed essential shrinkage of the conjunctiva with some vertical symblepharon (Fig. 3). There was an immature cataract in the right eye and a mature cataract in the left eye. The Schirmer's test revealed 15 mm. of wetting in the right eye and 3 mm. in the left eye after five minutes.

A split thickness mucous membrane transplant from the lip was applied to the right lower fornix with excision of the subconjunctival scar tissue and cleansing of the sclera. A cuff of a rubber glove was put in place to maintain the lower fornix during healing. On discharge there was a good fornix and the graft was well healed.

One month later she was re-admitted to the hospital for surgery on the left eye. There was still a deep fornix in the right eye, but an ulcerated area was noted on the soft palate. The operation consisted of removal of the subconjunctival scar, with cleaning down to the sclera. A split thickness mucous membrane transplant was done with a rubber conformer in place. At the time of discharge from hospital there was a good lower fornix.

The patient was seen again in June 1960. A recurrence of the symblepharons was noted in the left lower fornix (Fig. 4) and ulceration of the soft palate was still present. The entropion and trichiasis in the right eye were corrected by a modified Wheeler type II and Hotz skin muscle procedure. She was admitted to hospital again in July 1960. Vertical adhesions were noted in both lower fornices, which were contracted. Some contracture made it difficult for the patient to turn her eyes to the left. Riolan's muscle was excised from the left eye to correct the entropion and trichiasis. Postoperatively there was some subjective improvement.

The patient was re-admitted to hospital on December 12, 1960, when the vision in the right eye was 20/400 and in the left eye it was reduced to accurate light perception. Marked trichiasis and cicatricial entropion were still present. In the left eye there were marked vertical symblepharons in the lower fornix. Both corneae showed superficial opacities and keratitis. A separation of the symblepharon of the left lower fornix was done and an impression was taken for scleral contact lenses, which were inserted in both eyes. Efforts were made to make the contact lenses comfortable and to prevent continuation of the disease; however, the symblepharons progressed in the left eye, marked erosion of the cornea developed with folding of Descemet's membrane and the development of a superficial vascular pannus.

The patient was seen again in April 1961. She was wearing her contact lenses comfortably in both eyes; the fornix was good in the right eye and fairly good in the left eye. The disease seemed to be arrested at that time, and the patient was comfortable but the eyes were slightly injected.

CASE 3.—J.T., a white man aged 62 years, was admitted to hospital on January 21, 1960, with a one-year history of crusting and bleeding of the nose which was resistant to medical treatment. For the preceding six months the left eye had become progressively irritated and the lids had become swollen.

In the nose the anterior mucosa was atrophic and crusting and bled easily, but no characteristic lesion was noted. The vision in the right eye was 20/30, in the left eye 20/20. Entropion and trichiasis were present in the left eye and there was some lid edema and swelling of the conjunctiva. There were also a few small ulcerations on the conjunctiva and tarsus of the left lower lid as well as vertical symblepharon. The right eye did not appear to be involved. The lacrimal secretion was markedly decreased and the Schirmer's test showed 4 mm. of wetting in the right eye and 5 mm. in the left eye after five minutes.

The cultures from the conjunctival sacs were negative, the scrapings of the conjunctivae showed no inclusion bodies and there was no eosinophilia. A biopsy of the conjunctiva showed that the stroma beneath the epithelium was infiltrated with plasma cells, lymphocytes and histiocytes; a few polymorphonuclear leuko-

cytes were evident, there was abnormal proliferation of fibroblasts in the stroma and one area of ulceration was noted.

The patient was treated symptomatically with local application of corticosteroids and antibiotic ointments and electrolysis of the ingrowing lashes, with relief of the symptoms.

CASE 4.—N.D., a 70-year-old woman, had a history of metastatic involvement of the spine which was treated with cobalt radiation in 1953 and a mass in the suprasternal notch, also treated with cobalt radiation; she had a squamous-cell carcinoma of the tongue which was treated with radium in 1957 and removed surgically in 1958. The patient was admitted to hospital in November 1958 with a five-year history of intermittent blurred vision which was gradually worsening. Both eyes had been dry but latterly there were some tearing and photophobia in the right eye.

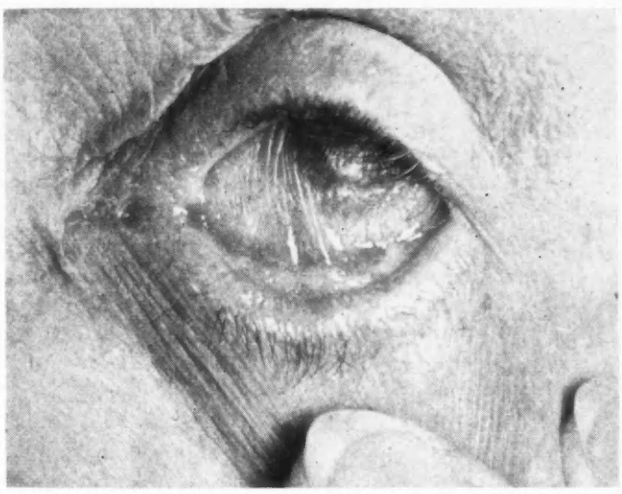

Fig. 5.—Case 4, left eye reveals a dry cornea and conjunctiva with vertical symblepharon.

There was no evidence of systemic involvement with pemphigus. The vision was limited to the detection of hand movements by the right eye and faulty light projection in the left eye. For some years pemphigus had affected the conjunctiva and cornea of the left eye and more recently the right eye. The conjunctiva of both eyes was injected and vertical symblepharons were present bilaterally but much more marked in the left eye (Fig. 5). The left eye was dry with deficient lacrimal fluid due to obstruction of the lacrimal gland ducts, the cornea was dry with complete vascularization and the adduction movement of the eye was limited. In the right eye there was a deficient precorneal film with diffuse punctate staining and some superficial vascularization was starting around the entire limbus. There was also a small depression in the centre of the cornea. The lacrimal secretion as measured by the Schirmer's test was: right eye 18 mm. and left 0 mm. wetting.

Scrapings of the conjunctivae did not contain eosinophils and there was no eosinophilia. The patient was treated with local corticosteroid therapy and 1% methyl cellulose drops.

In February 1960, a central corneal nebula was noticed in the right eye, and the vertical symblepharons in the lower fornix had increased. The left eye was still dry. A cataract extraction performed on the right eye improved the vision to 20/200.

CASE 5.—G.H. was admitted to hospital in March 1960 with a two-year history of redness, chronic irritation, photophobia and lacrimation in the left eye. For about six months she had been complaining of similar symptoms in her right eye. She had been treated for recurrent lesions of the mouth for two years. The vision was 20/25 in the right eye and 20/30 in the left. In the right eye, there were two vertical symblepharons, one in the lower and the other in the upper fornix. In the left eye vertical adhesions were present in the lower and upper fornices, more marked than those in the right eye. A superficial vascular pannus was invading the left cornea nasally and from below. Ulcerations of the buccal mucosa were present.

On March 31, 1960, a split thickness mucous graft was performed with tissue taken from the lower lip; the scar tissue was removed and sent for pathological examination. The specimen was composed of fibrous material, blood vessels, occasional chronic inflammatory cells and a few polymorphonuclear leukocytes. As there was no epidermal tissue, it was difficult to make a diagnosis of pemphigus. The postoperative result was satisfactory and good fornices were obtained.

CASE 6.—E.N. was admitted to hospital with a history of chronic irritation and lacrimation in both eyes but worse in the left, for the past eight or ten months. She had ulcerated areas on the soft palate and throat for four years, which had become worse in the last year.

Her vision was correctable to 20/25 in both eyes. There was virtually no lower fornix in both eyes, owing to scarring and symblepharon. Some entropion was present in both eyes, worse in the left. Superficial punctate staining in the lower half of both corneae was noted. An area of ulceration of about one inch in diameter was found on the right anterior and posterior tonsillar pillars. In June 1960, a split thickness mucous membrane transplant from the lip was applied to the left lower fornix. The scar tissue was dissected and removed. On pathological section no epithelium was demonstrated and the specimen was entirely composed of fibrous tissue with no apparent inflammation. Two months after operation a fairly deep fornix was present.

CASE 7.—S.S., a 62-year-old Italian, first complained of mild irritation and discharge from both of his eyes in 1944. In 1946 a tarsectomy was carried out in both upper lids for what was believed to be trachomatous scarring. In July 1959, he was admitted to hospital still complaining of chronic irritation and marked decrease of vision in both eyes. The vision was reduced to counting fingers at two feet with the right eye and to 15/400 in the left eye. There was an inadequate closure of the lids in the right eye and trichiasis was noted. The tarsus had been removed from both upper lids, and mild ulceration on the upper palpebral conjunctiva was found. Vertical symblepharons were present in both lower fornices (Figs. 6 and 7). There were superficial scarring and superficial vascularization on both corneae; the surface epithelium of the right cornea was irregular and crinkled on the nasal margin (Fig. 8). The lacrimal secretion was decreased in both eyes and by the Schirmer's test there

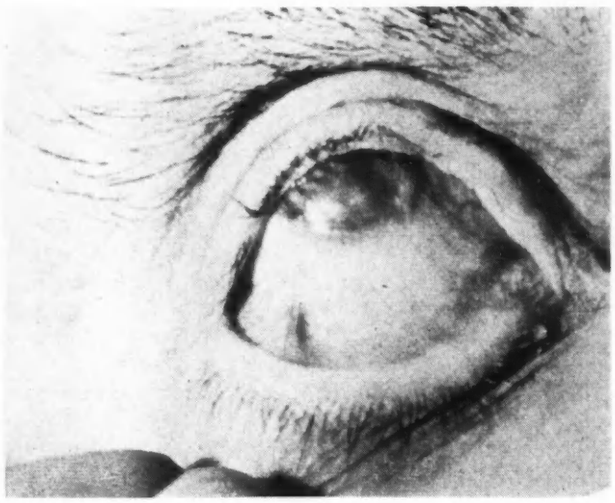

Fig. 6.—Case 7 shows the vertical symblepharon in the right lower fornix.

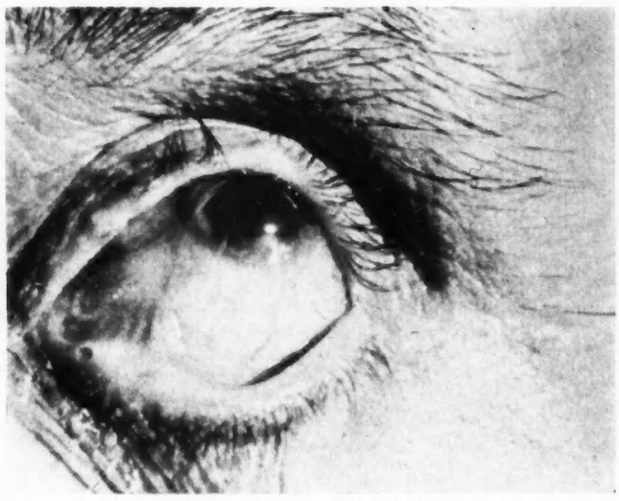

Fig. 7.—Case 7 illustrates the symblepharon in the left eye.

was 8 mm. of wetting in the right eye and 3 mm. in the left eye after five minutes. The bacteriological cultures were negative, and the scrapings of the conjunctivae showed only a few polymorphonuclear leukocytes and no other inflammatory cells. There was no eosinophilia. A biopsy of the conjunctiva showed that the subepithelial stroma contained moderate numbers of chronic inflammatory cells, including numerous plasma cells. On September 10, 1959 a lamellar keratoplasty was done on the left eye and in April 1960, the vision in that eye was correctable to 20/50. A vascular pannus progressed from the nasal area and in October 1960 when the eye was irritable and red, the pannus had reached almost to the pupillary area and the vision was decreased to 20/100 (Fig. 9). The inflammatory process cleared up, and in January the eye was white, and quiescent, and the vision had improved to 20/60.

DISCUSSION

The etiology of pemphigus is unknown, although infection with a virus is suspected to play a role. Various theories such as the action of toxins, constitutional influences, allergies and specific enzymes have been considered, but none of these have been definitely incriminated.[2]

In none of the reported cases of pemphigus did the individuals develop an eosinophilia; also eosinophils have not been found in any of the conjunctival scrapings. In this series, only Case I was receiving steroid therapy at the time of examination.

Although the lower fornices are involved as a rule, in Cases 1, 5 and 7 the upper fornices were also damaged by the disease in its early stages.

The treatment still leaves much to be desired. The lamellar keratoplasties, though technically successful, may be re-invaded by the vascular pannus or become opaque from irritation and desiccation. Dissection of scar tissue takes place, and split thickness mucous membrane transplants are frequently ill-fated because of the progressive character of the disease. The scleral contact lens may be of some advantage in arresting further damage to the cornea and conjunctiva; however, our experience with this form of treatment is limited.

SUMMARY

A classification of pemphigus as it involves the eye has been outlined. Acute and chronic pemphigus are

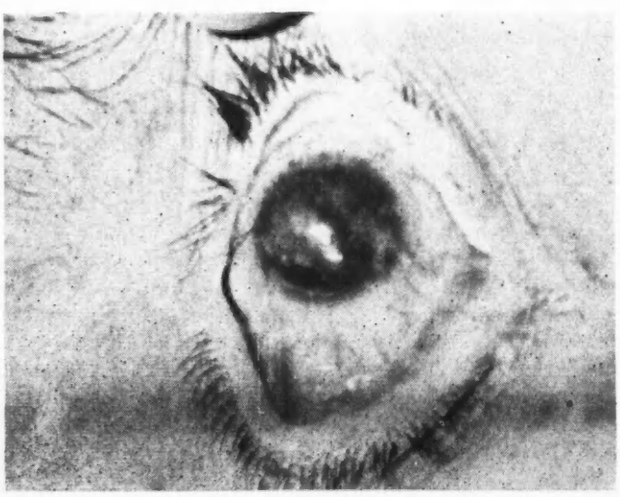

Fig. 8.—Case 7. There is superficial scarring and vascularization on the cornea. The surface epithelium is irregular.

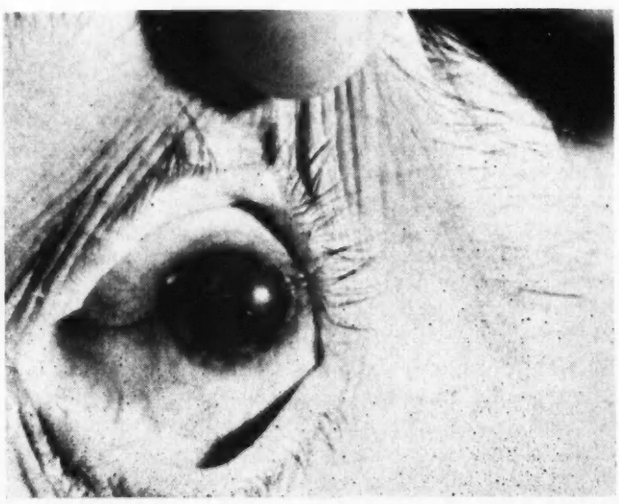

Fig. 9.—Case 7, one year postoperatively. The vascular pannus has progressed over the graft nasally.

the only types of systemic pemphigus which affect the eye. Ocular pemphigus and its pathology have been described. It is considered to be an entity separate from systemic pemphigus.

Seven cases of pemphigus with ocular involvement are presented.

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SPECIAL ARTICLE

BILIARY SURGERY IN SWEDEN*
THE LISTER LECTURE

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Stockholm, Sweden

IN THE autumn of 1867 a young surgeon from the Serafimer Hospital in Stockholm set out on a journey through Europe to study surgical methods in other centres and turned up at the Lister Clinic in Glasgow during the month of January 1868. From there he sent a letter to his chief, Professor Santesson, which was read aloud during a speech which the latter made before a meeting of the Swedish Medical Association and in it he was able to report that Listerian methods were already being applied at his hospital; these ideas were put into effect throughout Sweden at an early date. Lister's noteworthy paper "On the Antiseptic Principle in the Practice of Surgery" was published in *The Lancet* in the autumn of 1867, and his principles were introduced into Sweden only six months later. In Stockholm, compresses soaked in carbolic acid were used in clean wounds, while the carbolic acid spray recommended by Lister was used on open, infected wounds. From the very start the results were so favourable that surgeons gained increasing confidence, though this became evident only gradually in the number and quality of the operations.

Abdominal operations were restricted to herniotomies throughout the 1870's. In a history of surgery written a few years later, Santesson said, "Lister's antiseptic compresses have been tested all over the world and proved superior to all other means of preventing suppuration, or reducing it to a minimum. In Sweden they have been used since the beginning of 1868, and found to be highly effective. The contrast to earlier results in this respect is so striking, and the effect of treating wounds by that method so beneficial, that I do not hesitate to place it on a par with narcosis and endoscopy as one of the most important advances of surgery in my time." Santesson concluded by expressing the following heartfelt appreciation of Lister: "It is true that our contemporaries have made great achievements in the field of surgery, and we can with confidence leave it to our successors to continue our work, but it must not be forgotten that a lasting debt of gratitude is owing to this pioneer." The sterilization advocated by Lister in the 1870's did not cause any fundamental change in surgery in Sweden, and these first signs of the approach of the golden age of surgery were barely recognized there.

However, in other parts of Europe the new ability to achieve antisepsis and asepsis had encouraged surgeons to overstep one of the outer boundaries of surgery of that time, the peritoneum. On July 15, 1882, the first cholecystectomy was performed by Carl Langenbuch at the Lazarus Hospital in Berlin. When this case was published in the *Berliner Medizinische Wochenschrift* in the autumn of the same year, Langenbuch wrote that he had solved the problem of biliary surgery from three points of view: physiologically, as he had known even before operating that a human being, like the elephant, could do without a gallbladder, and technically and clinically, as his patient had survived and recovered. It is mentioned particularly in Langenbuch's paper that the patient felt fine the morning after the operation and had lit a big cigar, the symbol of elevated serenity and well-being! Yet Langenbuch's report did not capture the imagination of the surgeons, and the "cholecystectomists" had to submit to a protracted and

*Presented at the 94th Annual Meeting of the Canadian Medical Association, Montreal, June 1961.
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violent scientific debate with the "cholecystostomists", who insisted that only the extraction of stones and drainage was justified. In Sweden the first cholecystectomy was not performed until 1889, seven years after Langenbuch's report.

Furthermore, at the time of the first biliary operation in Sweden, enough experience had already been gained on the Continent to enable the Swiss surgeon Courvoisier to formulate his law, the accuracy of which has since been confirmed by several generations of surgeons: "When the common bile duct is obstructed by a stone, dilatation of the gallbladder is rare; when the duct is obstructed in some other way, dilatation is common." This weighty clinical observation was made by Courvoisier on the basis of the elementary case reports available at a time when only a few hundred biliary operations had been done in Europe. As late as 1900, only six biliary tract operations had been performed at the biggest hospital in Stockholm; all six were cholecystostomies.

Certainly times have changed, and today over 1000 cholecystectomies are performed yearly in the two clinics in the South Hospital, Stockholm. Diseases of the gallbladder have come to the fore in Sweden to such an extent that they might well be described as endemic. Operations on the gallbladder often predominate in everyday surgery, and at each surgical meeting there is always something to be said on the subject of gallstones. We cannot establish exactly when the considerable increase in the frequency of gallstones took place in Sweden, but a large increase in the number of patients with biliary tract disease presenting themselves at the surgical departments of this hospital took place soon after World War II. Although Sweden did not participate in the war, there was a considerable restriction on the available food supply within the country. Thirty years ago, postmortem studies showed that gallstones occurred in approximately one-tenth of the population in Stockholm; the incidence in the rest of Sweden varied from one place to another but seemed to be more frequent in rich and fertile districts. In 1960, one sensational study was reported of a postmortem survey from the biggest city in Sweden's richest province stating that gallstones were present in 42% of the population. It has generally been assumed that the increase in the frequency of gallstones can be ascribed to the prosperity of the people in the Swedish welfare state. However, in recent years investigations into the etiology of gallstones have, on the whole, ended in negative findings. No definite correlation has been found between hypercholesterolemia and biliary calculi.

There is much evidence in favour of a hormonal influence. Women are subject to biliary disease about 15 years before men; in the age groups above 60 years this sex difference is almost obliterated, the number of men with gallstones being equal to the number of women so afflicted.

The frequency with which biliary tract operations are carried out in Sweden is as follows: at the South Hospital, during the 1940's operations for gallstones increased from a few hundred per year to 500-700 per year and have remained almost constant at this level throughout the decade 1950-1960. The Karolinska Hospital has experienced a similar, though slower increase in biliary surgical procedures during the same period. These two hospitals are located in a capital city where the clientele may be selected to a certain extent. However, the same rate of increase is noted in another hospital in the north of Sweden, which by itself provides surgical services for a population that is almost constant in number; the number of patients currently operated upon at that hospital annually corresponds to the number of surgical cases in a five-year period during the 1940's.

About 10 years ago a girl was referred to me for biliary surgery from the pediatric clinic, because the surgeons in the pediatric department did not consider that they possessed sufficient training in biliary surgery. Now the situation has changed; recently a pediatric clinic in Stockholm presented a review of the largest series of gallstone cases in children that has ever been published anywhere in the world. Fifty-nine cases of gallstones occurring in children between six and 15 years of age have been operated upon at that clinic during a 10-year period. Hemolytic anemia had been considered to be the most common cause of gallstones in children but this impression is not confirmed in this Stockholm material; only three of these patients had hemolytic anemia. The other 56 suffered from the usual types of biliary tract disease; 10 patients had cholecystitis and four had stones in the common bile duct. The etiology of gallstones in children is as obscure as it is in the adult; in this series the entire 59 patients were all slightly overweight. At another hospital in Sweden, a girl four years of age was recently operated upon because of the presence of gallstones; the only peculiarity in her case was that although she never ate sweets she had a real mania for consuming butter by the spoonful.

A 15-year-old boy was operated upon recently at the South Hospital whose cushingoid habitus would seem to predispose to gallstones, considering the general concept that obesity and hormones are of significance in this respect. However, the most striking feature about him was his far-advanced biliary disease; he had about 30 stones in the common bile duct, several of which were localized in the intrahepatic passages and were removed after repeated inspection with a choledochoscope.

Modern substitution therapy and antibiotics have enabled us to operate upon patients of advanced age for gallstones; to these may now be added children and young people, and so the range of biliary surgery is steadily widening.

SURGICAL INDICATIONS

There is often a striking lack of correlation between the pathophysiologic condition and the biliary symptoms. "Silent" gallstones have always been known to exist; postmortem examination has revealed a high frequency of biliary disease without symptoms. In Sweden, of those who have gallstones, it has been estimated that between 50% and 80% have few or no symptoms. The clinical type of biliary disease, in which gallstones pass through the cystic and the common bile duct, which was believed to cause the most severe pain, may occur without any symptoms whatever. It is particularly surprising that even severe cases of cholecystitis with perforation of stones into adjacent organs can take place without the patient's noticing anything untoward. Thus, a stone generally of a size preventing it from going through the cystic duct may perforate right through the wall of the gallbladder into a neighbouring organ, the duodenum or the transverse colon. In about one-quarter of cases of intestinal obstruction from a gallstone, no history of biliary disease is forthcoming. A rare occurrence, duodenocolic fistula, will illustrate the capricious behaviour of gallstones. This occurred in a man aged 60 who had had pain in the upper abdomen nine years before he was admitted to our hospital because of copious diarrhea; he was in very poor general condition. In hospital a fistula was located by radiographic methods, between the colon and the duodenum; the diarrhea was thus explained by fecal contamination of the small intestine. Surgery disclosed the fistulous tract through the gallbladder, walled in by the stones and by a severe pericholecystitis.

A large number of gallstones remain undiscovered during life and many others give rise to such minor symptoms that surgical treatment is never considered; this makes it difficult to lay down firm rules about indications for surgical intervention. We advise all *young* persons with abdominal symptoms that have been radiographically established to be due to biliary disease to submit to surgery. Earlier, there was a marked difference of opinion whether to recommend operation in patients with floating calculi but an otherwise properly functioning gallbladder. Surgery should be carried out in these circumstances because the majority of cases of gangrenous cholecystitis derive from these calculi, the size of a hazelnut or grape, that stick in Hartmann's pouch, occluding the gallbladder and causing stasis of the circulation of the organ.

One of the points of controversy in biliary tract surgery is the time at which severe cases of cholecystitis should be operated upon; Swedish surgeons favour an aggressive approach to treatment of cholecystitis. A careful analysis of 900 cases of acute cholecystitis has been made at one of our large hospitals in Sweden in the course of a 16-year period and the following recommendations for treatment are based on this study. Patients should be subjected to cholecystectomy *during the initial period* of this illness. The operation should be performed preferably within seven days of the onset of cholecystitis, after fluid imbalance and any existing cardiac or vascular disorders have been corrected. Today, patients with cholecystitis are very rarely sent home to rest until all symptoms have disappeared, to return for operation when the disease is in a quiescent state.

Intravenous cholegraphy is of considerable value in planning the treatment of acute cholecystitis. When the common bile duct is normal, without any visible calculi, and the passage to the duodenum is satisfactory, surgical intervention will probably involve cholecystectomy only, without any of the complications and risks to be encountered in the opening and exploration of the deep bile duct in infected cases.

An estimate of the correctness of the surgical indications in a series of cases, highly varied as to age, complications, other simultaneous diseases, etc., must be made on the basis of the surgical results. If the value of biliary surgery is weighed against the risks involved, such surgery can be discussed under three headings: the surgical mortality rate, overlooked common duct stones, and injuries of the common duct.

THE SURGICAL MORTALITY RATE

Of course the death rate has been considerably lowered in the 20th century in Sweden as elsewhere. The last survey conducted at the South Hospital covers the decade 1950-1959, in which the number of biliary tract operations (excluding those for cancer) was approximately 6000 and the surgical mortality rate was 1%. Operations performed because of stones in the common duct showed a high mortality rate (5%). Uncomplicated cholecystectomies on young and middle-aged patients have a very low mortality rate at the present time.

The following observations were made after an analysis of the specific fields in which improvements have occurred in the surgical mortality rate at the South Hospital. Deaths due to circulatory failure, thromboembolism, cholangitis and peritonitis are now less than 20% of the number which occurred in the decade 1940-1950; on the other hand, the deaths ascribed to technical mishaps in the course of surgery were about equal in the 1940's and 1950's, which suggests that technical skills have not increased in this period. However, biliary surgery can be performed today with a high degree of safety, and the complicated cases, chiefly those in patients over 60 years of age who have jaundice, account for most of the mortality.

OVERLOOKED COMMON DUCT STONES

Surgeons interested in biliary tract surgery have always agreed that stones in the common bile duct represent a major technical problem which is

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difficult to solve. As previously stated, stones in the common bile duct can pass through the ampulla of Vater without causing stasis and without producing symptoms. It may seem unnecessary to remove stones that do not produce stasis; however, there is no guarantee that such calculi will not give rise to severe complications such as cholangitis, jaundice, and pancreatitis in the postoperative period or later.

The technique of surgical cholangiography, introduced in Sweden five years after Mirizzi's first report in 1932, was accepted with such enthusiasm that in the course of two decades it has been applied in almost 100% of the patients treated at the leading university clinics and several of the smaller surgical departments. This occurred despite the fact that in several parts of the world this procedure is regarded as a time-consuming and not altogether harmless means of diagnosis. At the present time in Sweden there are surgical clinics with a total experience of more than 5000 surgical cholangiographies. In their practice, the main purpose of cholangiography is to establish whether or not there are any stones in the common bile duct; the frequency with which stones are discovered in the common bile duct by means of surgical cholangiography has justified continued use and improvement of this special technique. Stones in the common bile duct have been found in between 16 and 22% of patients studied by this procedure. This means that every fifth or sixth patient with biliary tract disease seen in the surgical department has a stone in the common bile duct. An alternative procedure may be followed, using cholangiography only in cases of jaundice or pancreatitis, and otherwise operating on a "common-sense principle" of estimating the calibre of the cystic duct and the common bile duct by palpating the latter, etc. The frequency of calculi in the common bile duct will then amount to about 10%. Thus, broadly speaking, calculi in the common bile duct would elude observation in every tenth case when surgical cholangiography is not used. Apart from establishing the high frequency of stones in the common bile duct, the regular use of surgical cholangiography has served to show that stones in the intrahepatic ducts are by no means rare; without cholangiography the presence of those stones would be unsuspected at operation. Intrahepatic stones not infrequently accompany a single papillary stone and may be the only calculi observed in the deep bile passages. The assumption that some common duct stones discovered postoperatively have arisen secondarily in the common bile duct should be viewed with some skepticism. Calculi can be formed in the deep bile ducts in cases of chronic stasis, for instance in the presence of strictures, but these consist as a rule of small, greenish-black, hard stones containing bile pigment and calcium, which differ entirely from the concretions containing mainly cholesterol, which are formed in the gallbladder and are discharged from there into the bile ducts.

Surgical cholangiography is also of value in providing a means of mapping out in detail the bile ducts and the anomalies existing therein; the surgeon can thus be forewarned of a low, more distal, confluence of the biliary ducts. If cholangiography is performed before freeing the gallbladder and before any ligation of the ducts, anomalies may be detected that otherwise might have led to injury of the deep ducts in the course of the operation. Another advantage of cholangiography is illustrated in the work of a Swedish surgeon who, by studies of thousands of cholangiograms, has found that the left intrahepatic bile duct has an almost horizontal course just along, or inside, the lower hepatic border. This finding has practical significance in reconstructive surgery after injuries to the common bile duct and secondary strictures; if, in postoperative strictures of the common duct, no extrahepatic bile ducts remain for anastomosis, the surgeon is able to prepare, free and open the dilated left hepatic duct for anastomosis to a jejunal loop.

Despite these advantages of surgical cholangiography, critical opinions of the procedure have been voiced. The time of operation is said to be unnecessarily prolonged, and however careful the examination, a certain percentage of errors occur; for example, large calculi concealed in the contrast medium are overlooked. Many have emphasized the risk entailed in injecting contrast medium into the bile ducts in patients with acute cholecystitis but this objection can be definitely rejected. The experience from these comprehensive Swedish studies would indicate that the risks of surgical cholangiography are very small. The author had an unusual experience recently when exploring a patient with pancreatitis and mild jaundice. Surgical cholangiography resulted in a very peculiar picture, and the roentgenologist was unable to decide if there were any stones. When the common duct was opened, a small flat "fish" jumped out, wriggled a bit, and died on the operating table. This parasite, *Fasciola hepatica*, had never been seen before in our surgical departments; it is a rarity in Sweden and most certainly also in Canada, but from what I have since heard, is common in China. The patient was the wife of a doctor, a refugee from Russia.

Five years ago, when cholegraphy (intravenous cholangiography) first came into use, it was believed that this new method might replace surgical cholangiography to a large extent; certainly, when the contrast filling is satisfactory, it can reveal clearly the presence of any stones in the deep bile ducts. If cholegraphy shows a small bile duct, 6 mm. or less, without any defects in the contrast, it is quite certain that there are no stones. However, from experience with a combination of cholegraphy and surgical cholangiography we have found that cholegraphy alone will not suffice to exclude the

possibility of stones in the common bile duct. When cholangiography has shown a common bile duct of a width of up to 10-12 mm. without any defects suggestive of stones, surgical exploration, in combination with surgical cholegraphy, will reveal stones in the duct. It is evident that cholegraphy is inadequate by itself for the exclusion of stones in the common bile duct. Nevertheless a widened bile duct will indicate the presence of a stone in the common bile duct, and this is the principle role of cholegraphy in biliary diagnosis. However, cholegraphy can also warn the surgeon of anomalies and assist him in avoiding accidental operative trauma to the bile ducts; for example, where the right and left hepatic ducts run parallel with one another in an extrahepatic course for a distance, or where the cystic duct opens into the narrow right branch of the hepatic duct.

However, the principal value of cholegraphy still lies in the discovery of any stones that may have been overlooked in the common bile duct during cholecystectomy.

INJURIES TO THE COMMON BILE DUCT

In Sweden the great increase in biliary tract surgery has resulted in an added number of injuries to the deep bile ducts. In recent years, this extremely serious surgical complication has attracted a good deal of attention among Swedish surgeons. In 1959, all the Swedish surgical departments reported the number of injuries in the common bile duct during the previous 10-year period, and allowed me to review the case reports; thus I was able to make a compilation of 240 cases of injuries to the common bile duct. At present, the population of Sweden is about seven million and about 21,000 cholecystectomies are performed every year. The annual reports from the hospitals and a special report on 18,000 biliary operations at six large surgical departments in Sweden showed a frequency of one bile duct injury during each 400-450 gallbladder operations. Many authors have assumed that the injuries to the common bile duct are generally attributable to a lack of competence in carrying out biliary surgery among young surgeons; for example, Cattell maintained that 90% of these biliary injuries could have been avoided for that reason. My study of Swedish cases does not support that opinion. The injuries to the common bile duct were evenly distributed among the chief surgeons, the staff surgeons and the youngest surgeons. However, the last were over-represented in the group of cholecystectomies that could be classified as simple operations. In the Swedish cases about 60% of the injuries to the common bile duct occurred in patients with complicated, indurative pericholecystitis, and the surgical reports gave a very strong impression of the great technical difficulties involved.

In the Karolinska Hospital, in a short period, we had seven cases referred to us because of injury to the bile ducts. They were all relatively young and thin women; the surgical reports did not indicate any particular surgical difficulties. In our opinion, the cause of all these injuries to the common bile duct was a phenomenon that we refer to as "tenting" of the duct. When operating on young persons who do not have cholecystitis or enough retroperitoneal fat to hold the bile ducts in a fixed position as in more corpulent persons, the slender deep bile ducts may, when the gallbladder is drawn upwards, follow suit, forming a tent. This may result in several centimetres of the common bile duct being cut away without the surgeon being aware of the complication. This "tenting" is a much more common cause of injury to the common bile duct than is currently believed; it is exceedingly important that all young surgeons become aware of this danger early in their careers because injuries to the bile ducts are a constant threat. In Sweden in recent years, four doctors have been sued by their patients in connection with injuries to the common bile duct but in none of these cases was suit brought against the surgeon for malpractice or negligence. Surgeons, like other physicians, cannot lay claim to infallibility and if, after due training, the surgeon acts according to the rules and principles of his profession, he should not be held responsible for complications due to technical accidents.

Cholecystectomies may have become very common, but they still call for extreme care and diligence. If a partial or complete section of the bile duct occurs, it can be repaired if discovered in time. Swedish experience shows that the prognosis for injuries to the bile ducts discovered during the primary operation is far more favourable than for injuries recognized postoperatively when biliary peritonitis or postoperative stricture develops. In the group in which the injury was discovered during primary surgery, immediate repair resulted in 70% recovery; in the group in which the injury was recognized during the postoperative course, only 32% recovered. The Swedish material has established that end-to-end anastomosis with good apposition of the mucous membrane provides the best results. If it is impossible to make an anastomosis without tension, the defect must not be replaced by a drainage tube and free transplants which result in a failure rate of 100%; instead hepatico-duodenostomy or hepatico-jejunostomy should be performed. All materials used for the anastomosis have, in common the tendency to cause obstruction after a time; therefore, all tubes must be removed at the earliest occasion considered safe by the surgeon. At the Karolinska Hospital we tried to use plastic material, Teflon, in the repair of several types of injury to the common bile duct but these materials, as well as rubber or vitallium tubes, also become the focus of obstruction after a while.

The average frequency of one bile duct injury in each 400 biliary operations is not representative

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of some of the leading clinics, where the ratio is much lower, about 1 in 1000. The mortality rate in the Swedish material from injuries to the bile duct during the decade 1950-1960 was very high. Every fourth patient died, half of them in the immediate postoperative period owing to hepatic insufficiency, hemorrhage and other complications. A system of referral of patients with bile duct injuries to a few large clinics, should be set up so that certain surgeons could specialize in this complicated branch of surgery; this arrangement is already partly carried out in Sweden.

Lastly, I should like to say a few words about percutaneous transhepatic cholangiography, a new diagnostic method which is being used in Stockholm at both the Karolinska and the South Hospitals. This method has been studied for some years in other parts of the world but it is not yet a part of routine diagnostic procedures. Transhepatic cholangiography is used principally in the differential diagnosis in cases of severe jaundice in which current radiographic methods are of no avail. Cholecystography and cholangiography call for good liver function which is absent in jaundice; this applies especially to cases where it is of the utmost importance for the surgeon to know in detail, before surgical intervention, the appearance of the biliary tree, especially in cases of injuries to the common bile duct in which a second operation has to be performed. Here, the surgeon is faced with a densely scarred operative field which is difficult to reach and very liable to brisk hemorrhage. Hitherto, for transhepatic cholangiography the technique commonly used was puncture from the anterior abdominal wall just below the costal arch, but this method has drawbacks including leakage of bile into the abdominal cavity. The surgeons of the South Hospital now make the puncture through the patient's lateral abdominal wall, in the centre of the hepatic outline, so that accidental lesions of the gallbladder can be avoided; this organ is generally distended in the presence of malignancy of the common bile duct. The examination is carried out in the x-ray department under general anesthesia and the instrument consisting of a needle inside a polyethylene catheter is inserted. The catheter is retained in the liver when the needle is withdrawn, and pressure measurements can be made through it from the intrahepatic bile ducts and the blood vessels if the tip of the catheter lodges in the latter; samples of bile can be taken for laboratory analysis. After evacuation of the bile from the hepatic tree, which is often under fairly high pressure, the contrast material is injected and repeated radiographic exposures are taken which give vivid and distinct pictures.

Our experience has demonstrated that much can be accomplished by this method: in difficult problem cases the correct diagnosis or important detail can be obtained through such a radiological examination, and in our opinion this method of examination, percutaneous transhepatic cholangiography, should be used to ascertain the anatomic details prior to operation in injuries of the common bile duct; for cases of jaundice of obscure etiology; and when the surgeon wants to know beforehand whether any stone or tumour is present after other methods of outlining the biliary tree have failed.

SUMMARY

A short account of the history of biliary tract surgery in Sweden, a discussion of some of the current problems in this branch of surgery, and some of the methods that have been developed to deal with them have been presented.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

CANCER OF THE STOMACH

For years roentgenologists have been photographing the stomach by what is known as the bismuth method, that is to say, they administer an ounce or two of bismuth, suspended in solution, and immediately take an x-ray of the stomach, and they claim that by this method they can distinguish the presence of a growth. In a recent paper, Cole and Einhorn advise the inflation of the stomach with air by inserting a tube, and injecting air with a Politzer bulb. Cole uses this because there are disadvantages in the use of the bismuth solution, in that it occasionally causes poisoning, and the shadow due to the bismuth may obscure that due to a tumour. They have used inflation a number of times with satisfactory results, but they do not suggest that it should replace the bismuth method, but that it should be used in conjunction with it, or if, for any reason, bismuth cannot be employed. Holtzknecht uses the bismuth method, and states that the presence of a tumour is indicated when (a) there are vacant spaces or defects in the contour of the mass in the stomach; (b) when there are abnormal boundaries of the mass; (c) when there are irregularities of peristalsis. If the tumour cannot be palpated, the demonstration of visible peristaltic waves from left to right is of importance, and still more so is that of peristalsis in the opposite direction.

As regards the diagnosis of disease of the stomach from abnormalities of peristalsis, it is a well-recognized fact that the most common site of carcinoma is at the pyloric end, where the peristaltic waves are strongest, and therefore most likely to be affected by induration of the stomach. In advanced cases, with extensive adhesions, the peristaltic wave is arrested at the site of the tumour. The diagnosis is most certain if the wave can be followed to the tumour, where it stops completely, and can be seen to begin again on the opposite side of the tumour. This is observed in cases in which the disease affects one curvature only.

In the presence of pyloric stenosis the waves are often unusually deep and frequent for a time, and may then cease entirely for an indefinite period, or reversed peristalsis may be observed.—Herbert A. Bruce, *Canad. M. A. J.*, 1: 805, 1911.

REVIEW ARTICLE

GIANT CELL PNEUMONIA AND MEASLES: AN ANALYTICAL REVIEW

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THE HISTOPATHOLOGIC features of giant cell pneumonia of infants and children are distinctive in contrast to the clinical manifestations of the disease. Nevertheless various misconceptions of the pathology are still current and a number of eponyms have been connected with the disease and, inevitably, have been misapplied. Further, the etiology of the disease has been a subject of controversy. While it has been firmly established that the disease develops in association with measles infection, some have implied that any of a number of viruses may be causal.

This report, which is based on the study of three cases at autopsy and on a review of the literature, is concerned first with a re-emphasis of the morphologic features; next, the pitfalls to histological diagnosis, especially those other lung changes, which, in our experience, may be mistaken for giant cell pneumonia; and, finally, with an analysis of the evidence for and against the concept that the measles virus is the only specific etiological agent responsible for giant cell pneumonia.

GIANT CELL REACTIONS IN MEASLES

Two types of giant cell may be found in measles infection in humans, the Warthin-Finkeldey giant cell and the syncytial epithelial giant cell. The former type is not a component of giant cell pneumonia but is discussed briefly in the following section, to distinguish it from the syncytial type.

Warthin-Finkeldey Giant Cell

This cell is found in lymph nodes or throughout the reticuloendothelial system and is considered to be specific for, and in fact diagnostic of, measles. The cell contains anywhere from a few to many small nuclei arranged in small morules or in a "grape-like" cluster, surrounded by a small amount of eosinophilic or basophilic cytoplasm (Fig. 1). The nuclei often resemble those of lymphocytes. The cells do not contain inclusion bodies, although in two reports[5, 41] these were stated to be present.

Generally credited with first noting the significance of these cells is Warthin, who, in 1931, found them in the tonsils removed from four children, all of whom subsequently developed measles within one to five days after tonsillectomy.[54] Finkeldey[25] described one similar case in the same year and these cells came to be known as Warthin-Finkeldey cells. Davidsohn and Mora[21] pointed out that this type of giant cell had been described earlier by Alagna.[6] Thus the eponym "Alagna cell" has sometimes been used in the literature.[14, 37] Alagna, however, stated that they resembled megakaryocytes, and did not attach any significance to the cells.

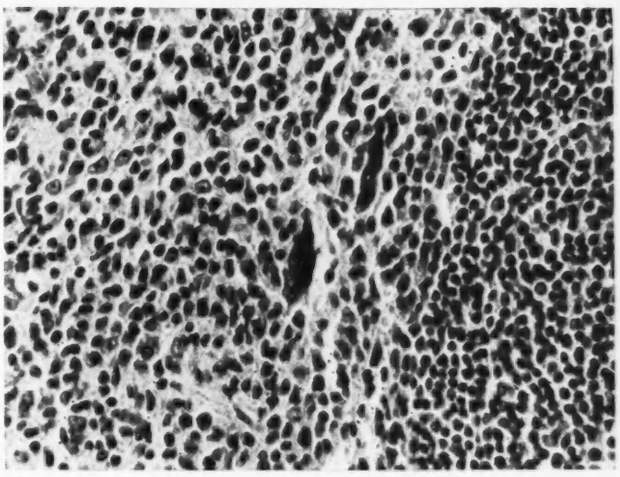

Fig. 1.—Warthin-Finkeldey cells adjacent to an appendix in a lymphoid follicle removed from a 9-year-old girl who developed a measles rash 4 days after operation (× 260).

In 1932 Herzberg found similar cells in the lymphoid elements of the appendix from a patient who, shortly after the appendicectomy, developed measles.[32] Many similar reports then appeared in the literature[10, 20, 21, 24, 29, 40-42, 47-49, 52] and, with few exceptions, these cells have been found during the prodromal phase of measles, a feature also noted in experimental measles infection in monkeys,[28] and they disappear soon after the onset of the rash. Although a number of theories have been proposed as to the histogenesis of these cells,[25, 26, 32, 40, 47, 48, 54] the exact mechanism of their formation is unknown.

Warthin-Finkeldey cells differ from the syncytial epithelial giant cell of measles, both in location and morphology. Although others[48, 49] have emphasized these differences, the syncytial type has still been referred to by some as the Warthin-Finkeldey cell.[19, 41]

Syncytial Epithelial Giant Cell of Measles in Giant Cell Pneumonia

The second type of giant cell sometimes found in fatal measles is the multinucleated type of epithelial origin. Inclusion bodies usually are found in the nuclei and/or cytoplasm. While they have been observed in various epithelial sites,[9, 24, 36, 47, 48, 50, 53] the cells are found most often arising from the epithelium of the lower respiratory tract. Interstitial pneumonitis in association with these pulmonary giant cells constitutes the chief morpho-

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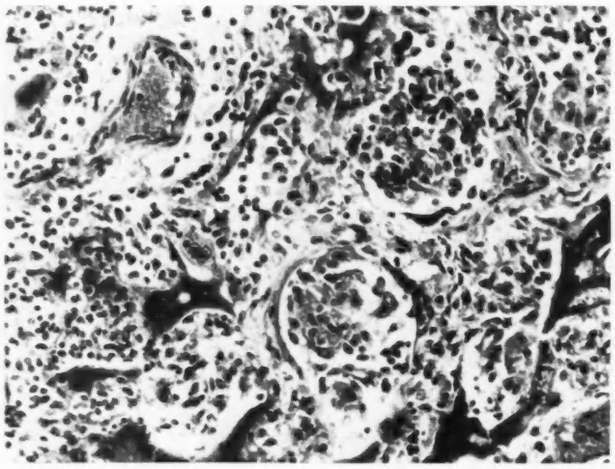
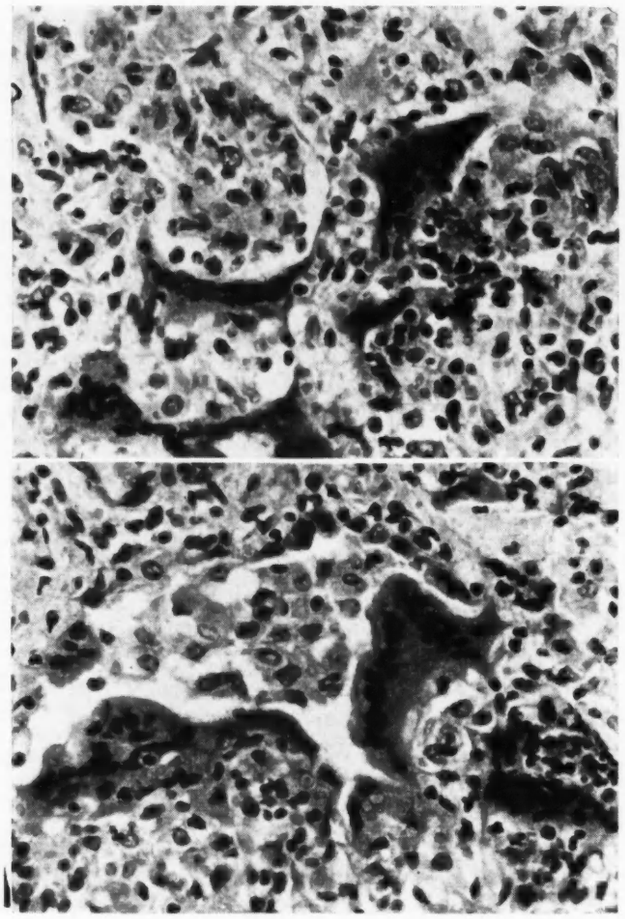


Fig. 2.—Multinucleated syncytial giant cells arising from, and partially encircling alveolar septa; marked interstitial thickening of alveolar septa and perivascular stroma are shown. Alveolar lumina are filled with masses of desquamated, hyperplastic alveolar cells (× 400).

logical criterion of giant cell pneumonia. Squamous or transitional cell metaplasia of bronchial epithelium may accompany these changes.

The giant cells are the most important diagnostic criteria of this pneumonia and are found in great numbers in all of the lung lobes (Fig. 2). They develop through focal or wide areas of proliferation of the epithelium of the air passages. An apparent disappearance of cell membranes occurs and thus syncytial, multinucleated cell masses of various sizes and shapes are formed in continuity with the remainder of the surface epithelium. As they develop in alveoli or alveolar ducts, small localized buds or knobs are formed which project into the lumen (Fig. 3). The giant cells may arise over a wider area to form flat, crescentic or scimitar-shaped masses (Figs. 4 and 5), often encircling the entire circumference of alveoli in a manner somewhat similar to hyaline membranes. Huge forms may be found, appearing to fill an entire alveolus (Fig. 6). In bronchi and bronchioles numerous giants cells tend to form over a wide area of the mucosa (Fig. 7). Many of the giant cells become separated from the lining epithelium and lie freely in the air spaces.



Figs. 4 and 5.—Both photomicrographs illustrate the varying sizes and shapes of the syncytial giant cells in alveoli. The continuity of the cells with the alveolar septa and their appearance contrast sharply with the desquamated cells in the lumina (× 800).

The number of nuclei varies considerably, ranging up to 40 or more in any one giant cell. The cytoplasm also varies in amount and is usually eosinophilic and often distinctly granular. In large

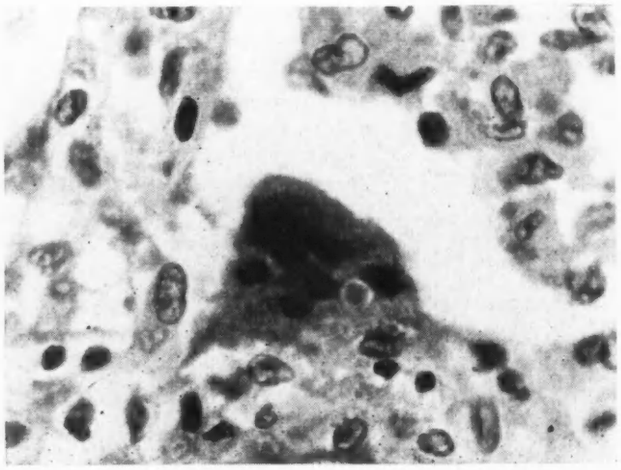


Fig. 3.—A small syncytial giant cell arising from an alveolar septum and projecting into the lumen. What appears to be a cytoplasmic inclusion body is actually a red blood cell in an alveolar capillary. Note thickening of alveolar septum at left (× 800).

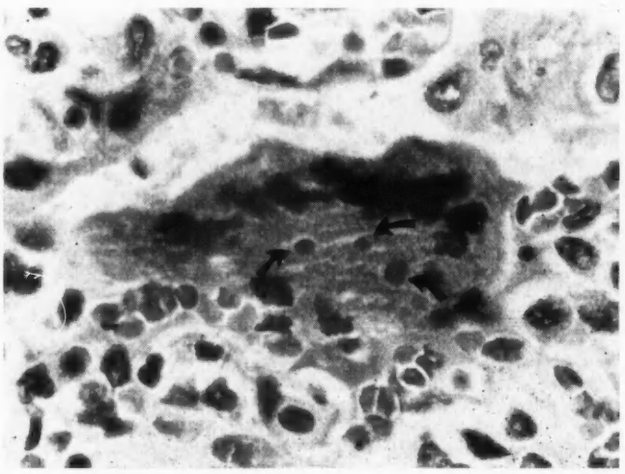


Fig. 6.—The syncytial giant cell shown fills the entire alveolus. Note the clumping and degenerative changes in the nuclei indicating an older giant cell. The arrows indicate cytoplasmic inclusion bodies (× 800).

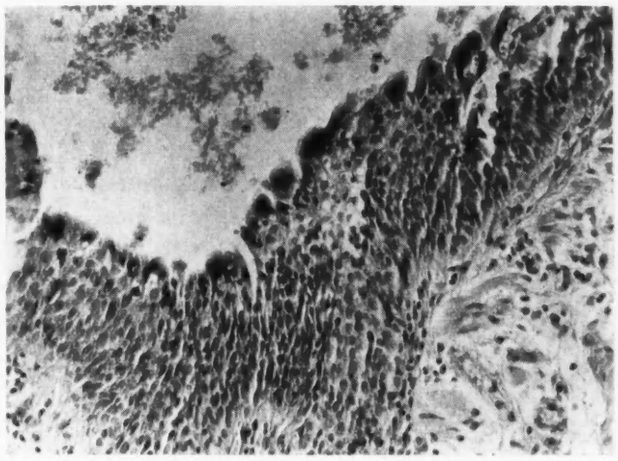


Fig. 7.—Hyperplasia and squamous metaplasia of the mucosa of a bronchus are shown. Small syncytial giant cells are situated along the surface of the epithelium (× 380).

or desquamated giant cells the cytoplasm becomes basophilic and tends to fragment.

Inclusion bodies, possibly viral antigen(s),[19] are an integral component of the cytological features. In giant cells containing few nuclei, intranuclear inclusions are small, round to ovoid, eosinophilic and surrounded by a pale zone which separates them from the nuclear membrane (Fig. 8). In larger giant cells, the inclusions may be amphophilic or basophilic and fill the entire nucleus, with margination of the nuclear chromatin around the inclusion body (Fig. 8). According to Sherman and Ruckle,[48] this basophilia together with clumping of nuclei (Figs. 6 and 8) represents degenerative changes in the cells. The cytoplasmic inclusion bodies are usually eosinophilic, round or oval, and also vary considerably in number (Figs. 6 and 8). Inclusion bodies, nuclear and cytoplasmic, are not necessarily confined to giant cells and can be found in alveolar or bronchial lining cells.

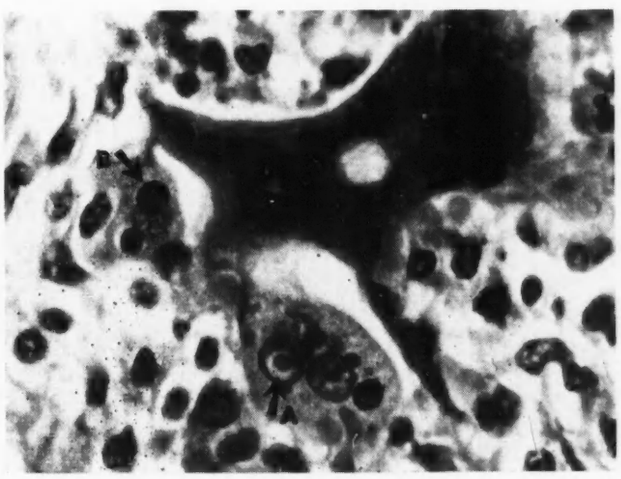


Fig. 8.—The variable appearance of intranuclear inclusion bodies, depending on age of the giant cells, is demonstrated. A small acidophilic inclusion surrounded by a "halo" (arrow A) probably represents the early appearance. The inclusion bodies become amphophilic, fill the nucleus and cause margination of nuclear chromatin (arrow B). In the large giant cell, the inclusions are basophilic and clumped. Cytoplasmic inclusions are seen in lower giant cell (× 840).

The severity of the interstitial pneumonitis is variable and may be associated with marked perivascular inflammation and fibrosis, and with abundant alveolar macrophages (Fig. 2).

Pitfalls to Histological Diagnosis

"FUSION" GIANT CELLS: These non-specific giant cells may be found in a variety of acute and chronic pulmonary diseases. They are few in number compared with the giant cells in giant cell pneumonia, and are found mainly in the lower lung lobes or in association with areas of bronchopneumonia. Others,[34] especially Moore and Gross,[39] have indicated that they represent fusion of desquamated pulmonary epithelium with alveolar exudates. The nuclei exhibit varying degrees of pyknosis, no true inclusion bodies are found and there is usually evidence of phagocytosis. The presence of these cells in varied conditions led Moore and Gross to conclude that giant cells in pneumonia have no specific cause. Such a conclusion is valid only if no distinction is made between these cells and the syncytial cells described above.

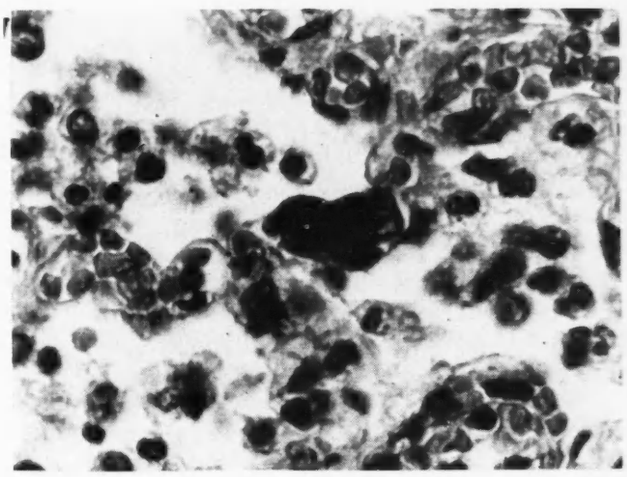


Fig. 9.—A megakaryocyte is shown within a capillary of an alveolar septum. The alveolar lumina, on either side, contain alveolar macrophages (× 840).

MEGAKARYOCYTES: Another giant cell which, judging from the published photomicrographs,[14, 37] is sometimes confused with the syncytial giant cell is the megakaryocyte which is found in alveolar capillaries from time to time in normal and pathological lungs and has no special significance. These cells are always intravascular. The nuclei are large, lobulated and stain a deep blue with hematoxylin (Fig. 9). Ciaccio[18] recognized occasional megakaryocytes in lung capillaries in eight cases of measles, but no special significance was attached to this finding.

OTHER VIRAL DISEASES: There may be a marked proliferation of alveolar lining cells in any viral pneumonitis. The aggregation of these cells in air spaces may mimic syncytial giant cells, and phagocytized debris or red blood cells resemble inclusion bodies. Similar phenomena may also occur in pneumonitis from other causes, including uremia.

THE LINKING OF MEASLES GIANT CELL PNEUMONIA WITH HECHT'S PNEUMONIA AND DISTEMPER PNEUMONIA IN ANIMALS

In 1910 Hecht described an interstitial pneumonitis and multinucleated giant cells in the lungs of 27 children at autopsy.[30] The giant cells arose by epithelial proliferation and showed little or no evidence of phagocytosis. In 19 cases there was an antecedent history of measles.

Since that time many cases of giant cell pneumonia have been reported.[17, 20, 24, 36, 38, 41, 44-48, 50, 52, 55] Because of the clinical history in many cases, the relationship of the disease to measles was clear. In the absence of clinical evidence of measles, the disease has been referred to as Hecht's pneumonia. Prior to 1945 it appeared that these two forms of pneumonia were regarded as different entities. At that time Pinkerton, Smiley and Anderson[45] pointed out the morphological similarities between cases designated as Hecht's pneumonia and the giant cell pneumonia sometimes found in fatal measles. A similarity to the giant cell pneumonia of minks, foxes and ferrets dying of distemper disease was also noted. Corbett[20] recorded similar observations in the same year.

Adams[2-5, 33] and his group had also been impressed with the morphological and certain clinical similarities between some acute respiratory diseases in humans on the one hand and distemper infections in animals on the other. Subsequent immunological studies appeared to lend support to the implication of these observations, namely that of the role of the distemper virus in giant cell pneumonia in humans. It was shown that batches of human sera and gamma globulin contained neutralizing substances against distemper virus, in titres as high as those known to exist in immune ferret serum.[12, 33, 35]

In summarizing the literature up to 1958, the impression is gained that where clinical measles had been present in association with giant cell pneumonia, the lesions were directly attributed to the measles virus. But since not all patients dying with giant cell pneumonia had clinical measles, the pneumonia was often referred to as Hecht's pneumonia and another virus was felt to be causal, such as the distemper virus or others.[3] It should be pointed out, however, that Pinkerton, Smiley and Anderson[45] considered the possibility that such cases of giant cell pneumonia might have been caused by the measles virus in persons in whom the rash did not develop.

Vitamin A deficiency was considered by Chown to be a possible factor in the pathogenesis of this disease. He noted other changes in the respiratory tract similar to those occurring in vitamin A deficiency.[17] Giant cell production in the lungs, however, is not a feature of vitamin A deficiency in either rats[57] or humans.[7]

DISCUSSION

Two major questions that arise in connection with this subject warrant discussion: the specificity of giant cell pneumonia for measles or other viruses, and the relationship or difference between Hecht's pneumonia and measles giant cell pneumonia.

Is giant cell pneumonia in humans pathognomonic of measles? Epithelial giant cells with intranuclear and/or intracytoplasmic inclusion bodies can occur in tissue cultures with a number of viruses: varicella, herpes zoster, herpes simplex,[8, 16, 56] measles,[3, 23, 48] distemper[3, 45] and a variety of adenoviruses.[3] The ability, however, to produce multinucleated giant cells both in tissue cultures and in the lower respiratory tract of humans appears to be a specific feature of measles.[16] Where a virus has been isolated in giant cell pneumonia it has been the measles virus.[24, 38, 48] Evidence that giant cell pneumonia might be provoked by other viruses has been less clearly established. Wolman and associates studied five cases of "interstitial giant cell pneumonia",[58] in none of which had there been clinical evidence of measles. They suggested that virus pneumonia of infants and giant cell pneumonia represented different phases of a single disease entity caused by a virus, although no virus was specified or isolated. It should be also pointed out that it is difficult to accept some of these cases as examples of giant cell pneumonia on the basis of the published illustrations.

Adams has accumulated extensive data suggesting that viruses other than measles may cause giant cell pneumonia. He described a form of epidemic pulmonary disease in infants ("primary pneumonitis") in 1941.[1] On later histological review of the case material,[3] pulmonary changes similar to those seen in giant cell pneumonia were found in three of nine fatal cases. It was felt that the disease was caused by a virus other than measles. Although no virus was isolated to support this contention, the clinical features were so characteristic that, in fact, another virus did appear to be causal. However, the statement that "conspicuous giant cell production in the lung appears to be a rather general viral phenomenon . . ."[3] must be examined more critically, particularly if, as it appears, this statement refers to the syncytial giant cell.

In considering the possible role of adenoviruses in giant cell pneumonia, Adams' observations on giant cell production with this virus were restricted to tonsils, adenoids and tissue cultures.[3] In contrast, in two recent reports of fatal adenovirus infection in humans, which were proved by isolation of the virus[15, 43] and in which interstitial pneumonitis and inclusion bodies were present, no multinucleated giant cells were found. The histopathology of the lungs in persons with fatal Asian influenza virus infection, proved by isolation of the virus, provides another instance of a viral pneumonitis in which giant cell production was not a feature.[31]

TABLE I.—TIME OF DEATH AFTER MEASLES RASH OR EXPOSURE AND THE PULMONARY DISTRIBUTION OF GIANT CELLS IN GIANT CELL PNEUMONIA OF INFANTS AND CHILDREN

Authors	*Clinical measles*	*Measles exposure*	*Time of death*	*Pulmonary distribution of giant cells*
Denton[22]	Present—3 cases		All within 3 days	Alveoli
Semsroth[47]		Positive	14 days	Bronchi, alveoli
Masugi and Minami[36]	Present		4 days	Bronchi, bronchioles
Chown[17]	Present, Case 5		24 days	Alveoli
Stryker[52]		Questionable	3 days after ? exposure	Bronchi, alveoli
Pinkerton, Smiley and Anderson[45]	Undiagnosed rash, Case 2		1 month after the ? rash	Bronchi, alveoli
Corbett[20]	Present		2 days	Bronchi, bronchioles alveoli
Palmer [44]	Present		About 17 days	Alveoli
Adams *et al.*[3]	Present—2 cases		Case 1— 10 days Case 2—17 days after prodromal signs	Alveoli, bronchioles
Roberts and Bain[46]	Coryza and Koplik spots		3 days after prodromal signs	Alveoli
Sherman and Ruckle[48]		Positive, Case 25	3 days	Trachea, bronchi, (*) bronchioles
	Present in borrowed case		15 days	Bronchioles, alveoli
Namiki[41]		Positive	13 days	Alveoli
Enders *et al.*[24]		Positive, Case 1	About 26 days	No specific localization (*)
Mitus *et al.*[38]	Present—2 cases		21 and 35 days	No specific localization (*)
Author's cases	Present, Case 1		25 days	Bronchioles, alveoli (both cases)
		Positive, Case 2	25 days	

(*) Measles virus isolated.

Other evidence which leads Adams to implicate multiple viruses in the etiology of giant cell pneumonia was the similarity of the lesions in canine distemper virus pneumonia and the immunological studies indicating the presence of antibodies against distemper virus in humans, as noted above. Further studies by Carlström showed that the immunological age pattern of canine distemper virus-neutralizing activity in human sera suggested that it was acquired by man as a result of infection,[12] presumably with the distemper virus. Since distemper virus can produce giant cells in natural as well as in experimental infections of animals, and since neutralizing substances against this virus have been found in humans, it might appear reasonable to assume that this virus might produce giant cell pneumonia in humans. There is, however, no definitely proved case (isolation of the virus) of naturally occurring distemper infection in man.

Interest in the group of distemper viruses as a possible etiological agent in giant cell pneumonia in humans was also stimulated by the immunological relationship that had been demonstrated between this group of viruses and the measles virus.[2-5] Such evidence suggests only that there is an antigen common to both viruses, although neither Cabasso, Kiser and Stebbins[11] nor Enders *et al.*[24] found any evidence of such an antigenic overlap in their studies.

According to Stowens,[51] pulmonary multinucleated giant cells have been found in culturally proved adenovirus A7 pneumonia. To date this has not been a specific or consistent finding in this pneumonia[15] and has been found in few cases, although in time it might be established that this virus is responsible for some cases of giant cell pneumonia. It has been emphasized, however, that the characteristic lesion in this adenovirus pneumonia is a severe necrotizing bronchopneumonia. Such a lesion is not a feature of measles giant cell pneumonia.

In its true form then, giant cell pneumonia in humans is a disease specifically associated with the measles virus. The implication[3] that it occurs with other viral infections in humans requires further supporting evidence.

While the main impediment in establishing the measles etiology of giant cell pneumonia has been the failure to isolate the virus in all cases, a no less pertinent problem is the absence of giant cell formation in all cases of fatal measles with respiratory involvement. Three of five cases of "virus pneumonia" reported by Goodpasture *et al.*[27] had prior clinical measles, but no giant cells were found. Pulmonary giant cells were also absent in some of Denton's cases[22] of fatal measles. Case 3 of Roberts and Bain[46] died three days after the development of the rash; while Warthin-Finkeldey cells were found in lymphoid tissue, no pulmonary giant cells were found. Roberts and Bain also referred to Kreider's report of 36 cases of measles in which death followed respiratory complications, but giant cell pneumonia was not found. In explaining the absence of giant cells in such cases, some have felt that secondary bacterial pneumonia may obscure the giant cell reaction,[46] or that as the disease becomes chronic the giant cells tend to disappear. Referring to Table I, however, it can be seen that giant cell pneumonia can be seen as long as 35 days after the rash.[38]

It must be noted that this table shows only the pulmonary distribution of giant cells in those cases of giant cell pneumonia where clinical measles or exposure was known to have been present. Thus in the column headed "Authors", the table does not include *all* the cases of giant cell pneumonia, *but only those reports which had a history of measles.* The table indicates the interval between

the time of clinical measles or exposure and the time of death. The time interval is important in estimating the duration or persistence of giant cells.

What is the difference, if any, between measles giant cell pneumonia and Hecht's pneumonia which occurs in patients with no evidence of clinical measles prior to death? This eponym also has been applied even when measles preceded death.[48] Both measles and Hecht's pneumonia refer to an interstitial pneumonitis with giant cell formation in alveoli, alveolar ducts, bronchioles and bronchi, and in fact measles was present in many of Hecht's original cases.[30] Since no morphological differences between the two have been defined and in the absence of proof of separate viral etiologies, there would appear to be no valid reason for maintaining a distinction through continued usage of the eponym. Sherman and Ruckle[48] seem to have suggested a difference between measles and Hecht's pneumonia on the basis of the distribution of giant cells. In their Case 25, from which the measles virus was isolated, giant cells were found in the trachea and bronchi; they were scarce in bronchioles and absent in alveoli. They compared these findings to those in another case designated as "Hecht's pneumonia" in a child dying 15 days after developing a *measles rash*, and pointed out that although the giant cells in this case were similar in appearances to those in their Case 25, the giant cells were concentrated in the alveoli and terminal bronchioles rather than in the bronchi. The implication that a morphologic difference exists between measles and Hecht's pneumonia depending on the basis of a differential distribution of giant cells is not supported by the findings in other reported cases (Table I).

Table I shows that in cases of giant cell pneumonia with measles, or with exposure to measles, the distribution of the giant cells is variable.

Sherman and Ruckle[48] suggested, however, that cases of giant cell pneumonia occurring without prior measles might represent infection with an atypical form of measles. One might agree with this in the sense that the clinical response to the measles virus might have been atypical in these cases, a point suggested earlier by Pinkerton, Smiley and Anderson[4] in 1945 and recently demonstrated by the isolation of the measles virus from three cases of giant cell pneumonia without clinical measles.[24]

Thus it would appear that many, if not all, cases of Hecht's pneumonia are the result of measles virus infection in which the typical clinical picture is masked. In many of these cases there had been an already existent chronic debilitating disease[17, 24, 45] which might have been responsible for the atypical host response.

Recent Literature

The most valuable contributions in elucidating the etiology of this disease have been made recently by Enders and Mitus and their groups.[24, 38] A virus indistinguishable from the measles virus was isolated at autopsy from each of three cases of giant cell pneumonia.[24] There had been no clinical manifestations of measles in these three patients. All had another serious illness. This report lends support to previous suggestions that (a) in cases of giant cell pneumonia occurring with other serious diseases (e.g. leukemia, mucoviscidosis) but with no clinical measles, the host response to the measles infection is altered, and (b) as the authors stated, "affords direct evidence for the etiologic role of measles virus in giant cell pneumonia". In the report of Mitus *et al.*,[38] the measles virus was isolated from two cases of giant cell pneumonia.

It was observed that there was an absence of antibody production in the two fatal cases in Mitus' report,[38] which emphasizes the altered or impaired immune response which may occur in this disease. In the two surviving patients, strongly suspected of having giant cell pneumonia on a clinical basis, there was depression of antibody formation. The administration of large amounts of measles antibody was the probable reason for their survival.[38]

SUMMARY

While it is apparent that there are certain divergent views regarding giant cell pneumonia, the following facts are evident:

1. Giant cell pneumonia is a distinct morphological entity characterized by the formation of syncytial, multinucleated giant cells, with nuclear and cytoplasmic inclusion bodies, arising from respiratory epithelium in association with an interstitial pneumonitis and, variably, squamous metaplasia of bronchial and bronchiolar epithelium.

2. Although future studies may support the contention that the disease develops in response to more than one virus, it is clear that the measles virus is a specific etiological agent and has been the only virus so far isolated from cases of true giant cell pneumonia in humans. Recently reported studies cast doubt on the role of distemper virus in the pathogenesis of this pneumonia in humans.

3. While giant cell pneumonia in patients who did not develop clinical measles has often been called "Hecht's pneumonia", there are no morphological differences between such cases and the giant cell pneumonia of measles. In the light of recent reports, it is likely that "Hecht's pneumonia" is caused by the measles virus in persons who do not develop the rash. The reason for this atypical host response is not clear although it has been reported in patients already afflicted with a chronic debilitating disease and/or with an impaired immune response.

In conclusion it is suggested that the term "Hecht's pneumonia" be discarded and that the disease be refered to as "viral giant cell pneumonia" the etiological classification depending on the virus isolated, since viruses other than measles may be causal, although to date there is little or no evidence that this is so in man. If no virus is isolated, then the disease might be termed "giant cell pneumonia with inclusions". In the latter situation, however, it would seem logical to invoke a measles etiology if a clinical picture of measles had existed prior to death and/or if Warthin-Finkeldey giant cells are found in lymphoid tissue at autopsy.

BRIEF SUMMARY OF THREE CASES*

CASE 1 (KUMC-2354).—Five and one-half weeks prior to death, J.W., a 14-month-old white male, developed fever, anorexia, weakness and marked anemia. These persisted for two weeks when periorbital edema appeared along with a fine maculopapular rash, which began on the face and spread to the trunk and abdomen. Shortly after this he was admitted to hospital, 18 days before death. One week before the initial onset of his illness, he was exposed to measles and received gamma globulin (0.5 ml.). Five siblings developed measles shortly after he was hospitalized. On admission there was periorbital edema, a skin rash over the face and neck consisting of small, 0.1-0.3 cm., slightly raised, reddish scaling areas, and slight hepatosplenomegaly. The body temperature was 101° F., the pulse 120/min., and respirations 30/min. The following investigations were carried out: the hemoglobin was 6.7 g. %; hematocrit 27%; leukocyte count 3250/c.mm. with a differential of 32% polymorphonuclear leukocytes, 65% lymphocytes and 3% monocytes; platelets 243,000/c.mm.; and a blood film showed hypochromia and microcytosis with 5% reticulocytes; the tuberculin and histoplasmin skin tests were negative; the serological and febrile agglutinins tests were negative; and tibial bone marrow showed erythroid hyperplasia.

Throughout hospitalization the patient's temperature remained elevated and the leukopenia persisted; the lowest count was 2700/c.mm. Five days before death, severe respiratory distress developed with a temperature of 104° F. Pseudomonas, non-hemolytic staphylococcus and pneumococci were cultured from throat swabs. Despite blood transfusions, antibiotic therapy, tracheostomy and oxygen, the patient expired in respiratory failure.

Giant cell pneumonia was found at autopsy. The giant cells were less numerous than those seen in other cases and were found in alveoli and ducts, and in scattered bronchioles. Many nuclear inclusion bodies were present but cytoplasmic bodies were rare. An acute bacterial tracheobronchitis and bilateral bronchopneumonia were superimposed. No Warthin-Finkeldey cells were found in lymph nodes, appendix, spleen or thymus. Bone marrow smears and sections revealed erythroid hyperplasia and a virtual absence of mature myeloid cells with promyelocytic hyperplasia. Megakaryocytes were normally plentiful. *Pseudomonas aeruginosa* was cultured from cardiac blood, spleen and various levels of the respiratory tract. Studies carried out on specimens of lung, spleen, lymph nodes, brain and cardiac blood failed to reveal any virus.

Comment.—Although no virus was isolated, a measles etiology for the giant cell pneumonia was assumed, because the patient was exposed to measles and developed the rash 3½ weeks prior to death. As noted earlier, giant cell pneumonia often occurs with measles infections in patients who are already suffering from a serious disease. Such a background in this case is difficult to determine although a severe anemia and moderate leukopenia were present. The bone marrow findings were compatible with leukemia according to some consultants, while others interpreted them as indicative of maturation arrest.

CASE 2 (VGH-A293-58).—D.R.P., a 17-month-old white male, was admitted to hospital 56 days before death with rhinitis, conjunctivitis, a cough, vomiting and diarrhea, all of two days' duration. Since the age of two months there had been recurrent eczema. At four months he was stated to have had "spinal meningitis" and pneumonia. The child had never received any immunizations. He weighed 20 lb. Physical examination revealed only slight dehydration and atopic eczema involving the face, neck, limbs and buttocks. The results of the laboratory investigations were: hemoglobin 9.8 g. %; leukocyte count 25,500/c.mm. with 44% eosinophils. The urinalysis, serum electrolytes, stool fat and trypsin were within normal limits. Topical hydrocortisone was applied to the skin lesions, and cortisone, 300 mg./day, was given orally, along with erythromycin 375 mg. daily. Twenty-five days prior to death, an outbreak of measles occurred in the patient's ward and he was given 2 ml. of gamma globulin, intramuscularly. An abscess developed in the left axilla, and *Staphylococcus pyogenes* was cultured from the pus. Tetracycline HCl (Achromycin) 375 mg./day was substituted for erythromycin. About two weeks before death, the temperature rose to 102° F. A few days later respiratory distress ensued and rales were heard in both lung fields. Chest radiographs revealed bilateral, patchy bronchopneumonia. Despite therapy, which included gamma globulin injections, the child expired in respiratory failure. During the last week of life, monkey kidney cells and suckling mice were inoculated with stool extracts but no virus was isolated.

Giant cell pneumonia was found at autopsy. Giant cells were numerous and were found arising from alveoli, alveolar ducts and bronchioles. Cytoplasmic inclusions were abundant but the nuclear type was scarce. Warthin-Finkeldey giant cells were found in hilar and mesenteric lymph nodes.

Comment.—The assumption that the measles virus was the etiological agent in this case is based on the finding of Warthin-Finkeldey giant cells in the lymph nodes at autopsy with the historical background of exposure to measles. The clinical history of repeated infections suggests hypogammaglobulinemia, but no laboratory determination of the plasma globulin levels was carried out. Whether the administration of gamma globulin altered the clinical response (rash) to the proposed measles infection is speculative.

CASE 3 (VGH-A253-56).—A.Mac.D., a 2½-year-old white male, was first admitted to hospital 13 months prior to death with a history of repeated episodes of bronchitis since two months of age, and intermittent diarrhea which was initiated or aggravated by table sugar, fruits and vegetables. The child had up to 10 bowel movements per day and the stools were either liquid or formed and soft, of a greenish or brown colour and always foul smelling. Investigations at that time revealed normal stool trypsin and salivary chlorides. One month before death he apparently developed a "staphylococcal pneumonia" and shortly after was readmitted to hospital. The weight was 22 lb. and temperature 99.6° F. Rhonchi and rales were heard in both lungs. The results of the following laboratory investigations were: hemoglobin 10.7 g. %; leukocyte count 8250/c.mm.; chest radiograph showed the presence of bilateral bronchopneumonia; and an examination of duodenal juice revealed trypsin digestion of gelatin at a 1:800 dilution. Four days before death the child became severely dyspneic and cyanotic. The temperature rose to 102° F., and roentgenograms re-

*The autopsy data and materials of Cases 2 and 3 were supplied by Drs. K. Aterman and C. D. Chipman, Pathological Institute, Halifax, N.S.

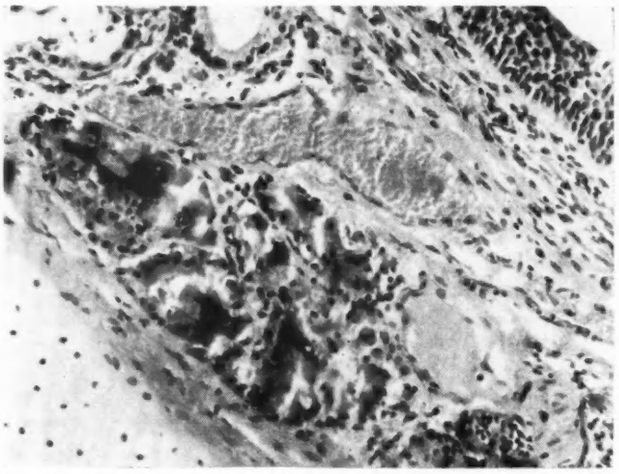


Fig. 10.—A segment of a bronchus is shown with cartilage at lower left and mucosa, showing hyperplasia, at upper right. Small syncytial giant cells are present in bronchial glands (Case 3. × 420).

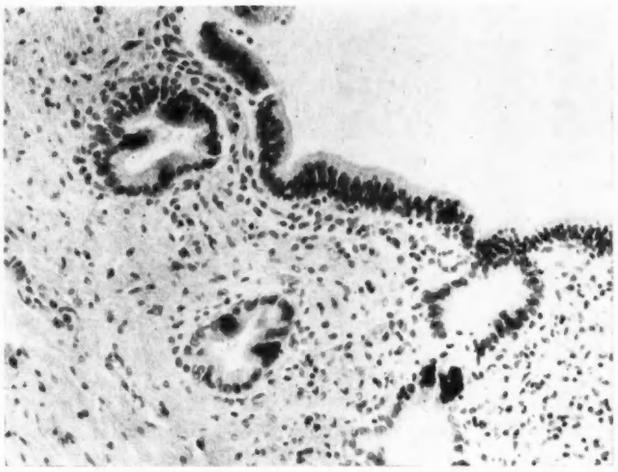


Fig. 11.—Small multinucleated giant cells arising from epithelium of pancreatic ducts (Case 3. × 400).

vealed extension of the pneumonic changes. The patient died in respiratory failure. Therapy had included cortisone, penicillin, novobiocin (Albamycin) and oxygen.

Giant cell pneumonia was found at autopsy. Giant cells arose from alveoli, alveolar ducts, bronchioles and occasional bronchi. Similar giant cells were found in numerous bronchial glands (Fig. 10). There was squamous metaplasia of both respiratory epithelium and bronchial glands. The peribronchial lymph nodes contained Warthin-Finkeldey cells, a few of which were also present in mesenteric lymph nodes. Small multinucleated giant cells were also found arising from the epithelium of large pancreatic ducts (Fig. 11), and from the epithelium of the colonic and gastric mucosa. No inclusion bodies were observed in these cells. There was no evidence of mucoviscidosis in the pancreas or lungs.

Comment.—Because of the finding of Warthin-Finkeldey cells it is assumed again that the measles virus was responsible for the giant cell pneumonia in this case. The clinical history of repeated chest infections and chronic diarrhea suggested mucoviscidosis or celiac disease. Duodenal juice contained adequate trypsin levels, however, and autopsy failed to confirm the diagnoses. While squamous metaplasia was found in the bronchial mucosa and glands, it was associated with giant cell formation, which is not a feature of mucoviscidosis. The pancreas was normal except for the striking presence of multinucleated, syncytial giant cells arising from large pancreatic ducts. This particular case is of interest in that giant cells were found not only in respiratory epithelium but also in bronchial glands, pancreatic ducts and the epithelium of the stomach and colon. Previously reported instances where giant cells have been observed in extrapulmonary sites include the epithelium of the appendix,[9] esophageal and pharyngeal mucosa,[36] lingual mucosa,[47] urinary bladder mucosa,[48] pancreatic acinar cells and hepatic cells[50] and nasal epithelium.[53] As well as reporting giant cells in the stomach, intestine, tongue and bile ducts, Enders *et al.* described giant cells, either multinucleated or mononuclear, with inclusion bodies, in the heart and bone marrow, although the cells of origin in these instances were not stated.[24]

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ADDENDUM

After this manuscript was submitted, a case of giant cell pneumonia in an adult has been reported (*Brit. M. J.*, 2: 288, 1961). Attention is also directed to a recently isolated virus group which is an important cause of bronchiolitis and pneumonia in infants. This virus group has been called the respiratory syncytial virus. The name derives from its cytopathic effect in cell cultures (see *Lancet*, 2: 473, 1961). As far as can be gathered, the histopathological changes induced by this virus in the respiratory tract are not known.

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GENERAL PRACTICE

THE DOCTOR AND THE SOCIAL WORKER

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IN 1946, when the World Health Organization formulated a definition of health as being a "state of complete physical, mental and social well-being and not merely the absence of disease or infirmity", it was hailed by those engaged in health work and related fields as something new, as "progress", a concept to be noted and acted upon. In essence, it is the distillation of thought concerning the dignity and value of mankind that is stated so simply in the Bible and expressed by philosophers from Hippocrates and Plato to the great humanitarians of our own time. Unfortunately, during the tidal wave known as progress, in which the magnification of the telescope and the microscope became increasingly more powerful, the emphasis on and the understanding of "the social well-being" of the individual became obscured.

During the latter part of the sixteenth century humanity started to become mobile and escaped into freedom and problems. But it was not until the middle of the nineteenth century that society's efforts for its own improvement began to take on the organized form that is known today as social work. Its earliest beginnings were amorphous and it was only fifty years ago that it was recognized that special educational skills or knowledge were required to help others in the social aspects of their living. The concern that stimulated the conscience of society and fostered the organization of agencies to give service to those who were in trouble or who were a threat to the community soon recognized that the impulse to do good and well-meaning intentions were not enough. Often, indeed, these attitudes alone led to more harm than good. Gradually, a body of knowledge and experience on which to base formal training was collected and developed until today the professional worker must have a Master's degree.

In the professional hierarchy, social work is "a Johnny-come-lately", and few know the extensive training and rigid requirements that the would-be social worker must meet. The body of professional knowledge, the skills, techniques and philosophy that must be learnt, absorbed and integrated, demand two years of postgraduate study at an accredited School of Social Work, so that the Master of Social Work practitioner has had at least six years' university training. However, when the formal learning period has been completed, the new social worker, like the newly graduated doctor, is just beginning to learn and for many years must receive careful help and supervision on the job. Old ideas die hard, but no longer are the benevolent Lady Bountiful, the on-the-shelf spinster, or the evangelist poking his nose in everybody's business, damned with faint praise by the name of "social worker".

Although it is true that social work has drawn knowledge from a number of disciplines, it has developed a methodology, skills and technique for helping that are particular to itself. The practice of these skills is directed toward four major goals as defined by Bowers:[1] (1) resolving or minimizing problems arising from impaired social functioning; (2) identifying potential areas of social dysfunction and initiating preventive measures; (3) aiding people to maximize their potential for social functioning; and (4) ensuring that resources be available appropriate to any of these goals.

Social service and social worker alike are concerned directly with the individual. Their purpose is to help modify the destructive factors in the environment that are acting adversely on the individual and to which he is reacting. Social work applies this method in three broad categories: casework, group work and community organization, but the emphasis is always on the individual—the individual acting and interacting in his environment. It is when this interaction becomes inap-

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propriate, or when factors beyond the individual's control or potentiality press in, that social well-being is impaired or lost and pathology of a physical, emotional or social nature, or a combination of all three, occurs. Because these three elements, distinct but inseparable, are manifest in every human being, one cannot be treated to the exclusion of the other two. This is done within and by means of a relationship, "that many-nuanced, finely graded thing". The social worker's focus is on the relationship *of* the individual to his problems *within* a relationship to the individual. But what, one may ask, is so special about that? Everybody has problems, everybody has relationships. Very true—so everybody has health and no one is immune to illness. And equally true, every illness does not need medical care of the expert variety. Everyone has a common cold and there are probably as many remedies as there are people—running the gamut from doing nothing about it to the use of the whole armamentarium provided by antibiotics. But let the common cold develop into something more serious—pneumonia or tuberculosis, and the experts are called in. Not everyone who has a problem needs help in a casework relationship: a few problems go away by themselves. Many more do not, and it is help with these that require professional skill. To carry this example further: if the cold were treated appropriately in the beginning, a more serious condition might not have developed. Just so with social problems: early recognition and expert help may well prevent marital discord from becoming a statistic in the divorce court, with ensuing maladjustment and heartache for all concerned.

The problems with which individuals need help run the whole range of human experience. Some require casework help for weeks or perhaps months; a few are solved in a relatively short time. For example: The A's who moved to the city a few months ago from the Middle West have no relatives near and only a few nodding acquaintances. Mr. A. is employed. The adequate but minimum income depends on his regular attendance at work. Mrs. A. has pneumonia and requires hospitalization and convalescent care, but who, in this frightening city, will care for brown-eyed Susie, aged three? There are resources in the community, several of them, and the social worker because of the specificity of her knowledge of community resources will know the one of choice. This sounds simple and it is, but it is more involved in procedure and application of knowledge and techniques than it sounds. The use of social service must be interpreted to both parents. Susie must be given explanations that she understands, and the individual in whose care she is placed must understand Susie. The social worker knows how and what to do in just such situations. The results are: Mr. A. will be able to continue on the job and visit Mrs. A. without adding his worry to hers as to whether or not Susie is "safe", and Susie is less forlorn and forgotten during the separation. Mrs. A. will rest more comfortably in her hospital bed and, hopefully, respond more readily to treatment and her use of the doctor's skill and knowledge. She will have contact with a social worker whose reports she is able to trust; her concern for her child will be lessened; and there will be no worry about the dreadful expense of a housekeeper at the $10.00 a day that they don't have.

A more complex problem that could not be solved so neatly and quickly is shown by the B's. Following a colostomy, the doctors and nurses diagnosed Mr. B. as "uncooperative", and referred him to Social Service because "he refused to learn how to do his irrigations" or "to adjust to hospital routines" and he was very "demanding". This too sounds simple—but the social record on the B's is 33 typed pages and shows weekly interviews over a period of eight months with both Mr. and Mrs. B. as well as frequent contacts with the doctor, the resident, two outpatient department clinics and three social agencies. Mr. B. learned to do his irrigations, accepted his illness and adjusted to returning to work slowly. At the same time, Mrs. B. was helped to accept the fact that Mr. B. was not going to make her an attractive widow immediately, that he would be around the house more and that their income would be reduced, at least for a while. Under all Mr. B's behaviour called "uncooperative" was a very poor marital adjustment—he just couldn't face going back home to a wife who, he knew, didn't want him. She did not want him when he was well and able to support the family, and be out of the house for 16 to 18 hours every day. On her part Mrs. B. was disappointed; her husband had been admitted for surgery for what she believed to be the fatal condition of cancer but had been so unkind as to recover. The solution to this situation was not easily found. However, the social worker helped the B's to find a way to re-establish at least as much equilibrium in their marriage as they had achieved before Mr. B's illness. How this was done and by what means is much too detailed for this presentation but represents long years of training, skill and experience. It is the job of the social worker to help the person with "the reality-facing side of life experience".

Because social workers deal with human beings in all aspects of their living, the doctor is a very important person to them in the performance of their jobs. So may the social worker be an important aid to the doctor. In our culture, the doctor occupies a role that is unique; he (or she) is considered an authority not only in matters of health and disease but in all affairs of living. A Master's degree thesis written recently at the School of Social Work, University of Toronto, revealed that of 30 doctors interviewed, about 75% recognized that their patients sought advice from them about social problems but 66% of them did not know where or how to obtain help or thought that social agencies were for the "poor". Social work is for everybody—not

only for the poor in purse but for the poor in spirit too.

This is an era of specialization that obtains even within the broad field of general medical practice. In the days of smaller communities and lower living pressures the general practitioner, who may not have known as much medicine, lived closer to his patient and their families. He knew from first-hand observation, to say nothing of his wife's gossip, when Mrs. X. would be in his office for a bottle of red medicine for her headaches because Mr. X. was doing his semi-annual stint in the local lock-up for his semi-annual binge, or when Mrs. Y. would take to her bed with vague pains because Billy was playing truant again. The family doctor was the family friend: he delivered the baby, stood by through the measles of childhood, dispensed salves for the acne of adolescence, counselled the young married couples, and closed the eyes of the grandparents in death. And it was his knowledge, so readily gained, of the facts of their lives that made the family doctor of a generation ago such a potent force for help. Time has changed and methods of practice are different, but people are the same. It is because of these same common human needs for understanding that the professionally trained social worker has value in helping people who are ill so that the doctor may use his medical skills more effectively.

The premise of collaboration and mutual sharing between doctor and social worker is not new. There are two medical schools in Canada who have on their teaching staffs medical social workers, and over 30 in the United States. Dr. James H. Means has said, "The complete diagnosis must be an epitome of all elements that enter into the clinical picture, social as well as biologic. It must include not only the disease but an understanding of the patient who has it."

The clinical entities, pneumonia in the corner bed or the Hodgkin's disease in the doctor's waiting room, cannot be separated from the persons who have them, nor can they be separated from the meaning of illness to them or to their families. Problems caused or accentuated by illness have many faces. The change of roles in the family constellation, the loss of status in the work world, the shift in relationships, and the tumult of guilt and anxiety within the patient are only a few. The effect of any or all of these can have a different meaning to every individual and to every family.

And over all looms the pall of fear. In his article "The Handicap of the Patient's Fears", Dr. Perry Pepper[2] wrote: "Fear is every doctor's enemy and every patient's bedfellow. Fear multiplies the social worker's problems, tests the nurse's tact and patience, lessens the doctor's chance to save." It is true that the doctor carries the greatest responsibility for lessening the patient's fears, but it is equally true that often because the doctor is the doctor, the patient and/or his family are unable to hear, to understand, or to offer the reason why he is afraid. To illustrate: A nervous middle-aged woman was referred to a social worker from a diabetic clinic because she was much more upset and anxious about her health than the clinician thought appropriate. The diabetes was mild and there seemed to be no reason why she should not do well on medication and diet. She told the social worker that she was sure she was dying and that she had sent to Europe for her sister to come to Canada to care for her three small children. Knowing the facts from the doctor and knowing that he had given careful explanation to the patient, the worker questioned why she felt the need to do this. The patient then explained that she had known two women in her home town who had diabetes, both of whom had died, therefore, it was fatal; she had diabetes and, therefore, she was dying and the doctor was not telling her the truth about herself. This called for further conferences between patient and doctor at which the social worker was present and in which the patient heard what was said, and cancelled her urgent call to her sister. She is doing very well.

Fear attacks members of the family too, as the following example shows. A young woman was brought to a large metropolitan medical centre from her home five hundred miles away for a mitral commissurotomy. She was accompanied by her husband, a professional man of no mean competence in his own field. The social worker saw the patient and her husband daily both before and after the operation; all seemed well, and the social worker was present on several occasions when the surgeon told the husband that the patient was making excellent progress and her condition left nothing to be desired. But every day he sought further assurance from the social worker, who simply reinforced what the doctor had already told him. He did seem uneasy but the worker did not think unduly so. Then the day came when, according to plan, he was to return to his family of young children and on this day he delayed the worker for over an hour, saying frequently that he hoped the patient would be all right and reminding the worker that she knew where to contact him at all times. Finally good-byes were said but an hour later the worker looked up from her lunch to find the husband standing beside her and he blurted out, "Has Mary lost her mind?" Suddenly, all was clear. Because of the heavy sedation the patient had been disoriented, but this simple explanation had not been given to the husband. The man had been consumed by the fear that his wife was now mentally ill and he had been too ashamed and frightened to ask the question directly; neither the doctor nor the social worker had recognized the real meaning of his repeated question "Will she be all right?" In many cases, patient and family are unable to express the reason for fears or feelings of inadequacy, even obliquely. The social worker, using her skills and techniques, one of which is a vertical and horizontal study of the

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family, is able to gain a knowledge and understanding, not only of the meaning of the current problem but how they have been able to cope with crises in the past and how they might be able to cope with the present one.

This working together of doctor and social worker demands acceptance and understanding on the part of each. These can be achieved only by a willingness to take the time and use every opportunity to get to know what the other is trying to do, how, why and when. Unquestionably, the how and why are relevant to the specific areas of competence: the when may be shared. Social workers are not competent to and do not give either a medical diagnosis or any statement as to probable length of illness or convalescence required, nor is theirs the decision on matters concerning management of the patient. There are many agencies and organizations under both private and public auspices, and collaboration with them may become tedious to the doctor if he has not learned something about them and if he has not given the social workers an opportunity to know him both as a person and a physician. The social worker has an obligation to know the doctor treating the physically ill client; the obligation of the doctor to know the social worker treating the socially ill patient is equally great.

If the patient is not known to a social agency and the doctor recognizes the need of social work help, it is always available. Each community has its own particular kind of agency organization, and a call to any one of them will locate a social worker who will help by:

1. Studying the way in which personal and environmental factors are affecting the patient.
2. Assisting the patient and his family to understand and cope with the new set of problems that seem to have appeared.
3. Helping them make use of the health and welfare resources available.

The social worker's equipment is intangible and invisible unless one counts the occasional box of facial tissues. Her tools are humanity and empathy, tolerance and acceptance, well seasoned with a sense of humour and stirred by a questioning mind. Her special knowledge is the meaning of human behaviour in terms of human needs baked in the mould of the wider community. Even so, social service is not a panacea for all human ills or a placebo for the cry of mankind. Nevertheless, social service applied in time may prevent "heart sickness from passing beyond a certain bitter point and the heart losing its life forever".

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CASE REPORTS

SOLITARY ABSCESS OF THE HEART* AN UNUSUAL CAUSE OF MYOCARDIAL INFARCTION

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THOUGH reported infrequently, myocardial abscesses are a well-recognized pathological entity.[1-5] They may complicate bacterial endocarditis[6] or overwhelming generalized infection, and have occurred as a solitary metastatic focus from a distant localized infection, e.g. osteomyelitis.[3, 7] Rarely, abscesses may form in a recent myocardial infarct, with rupture and sudden death.[4] In the following case, unique in our experience, fatal myocardial infarction occurred in a 22-year-old woman who at autopsy was found to have involvement of a major coronary artery by a solitary abscess of obscure origin.

Miss E.G., a 22-year-old night club dancer, entered hospital because of chest pain, dyspnea and cough. Two weeks earlier, stabbing pain began in the left chest which was unrelated to respiration, occasionally radiated to the left infrascapular region, and later became bilateral, accompanied by shortness of breath and a non-productive cough. Night sweats and orthopnea developed, the chest pain increased in severity, and the sputum was occasionally blood-stained. There were associated anorexia, nausea and vomiting. The attending physician noted the presence of a heart murmur during this period.

During the previous few months, fatigue had developed which was accompanied by weight loss of 7 to 8 lb. A year earlier, there had been a pregnancy, apparently complicated by postpartum infection but, except for this, the past history was non-contributory.

Physical examination revealed a thin, pale, slightly cyanotic white woman, sitting up in severe distress, coughing up small amounts of clear sputum. The throat was slightly injected. Respiratory excursions were limited and there was dullness at the right lung base, with scattered bilateral inspiratory and expiratory rales, maximal at the bases posteriorly. The point of maximum cardiac impulse was at the mid-clavicular line in the fifth intercostal space. A systolic thrill was felt over the entire precordium. A loud, harsh systolic murmur was heard in all areas, loudest at the third left interspace. One examiner noted a grade 2, blowing, early diastolic murmur in this region and down both sternal borders. The abdomen was tense, and the area of liver dullness was increased. Pelvic examination revealed a slight roughening, hypertrophy and tender-

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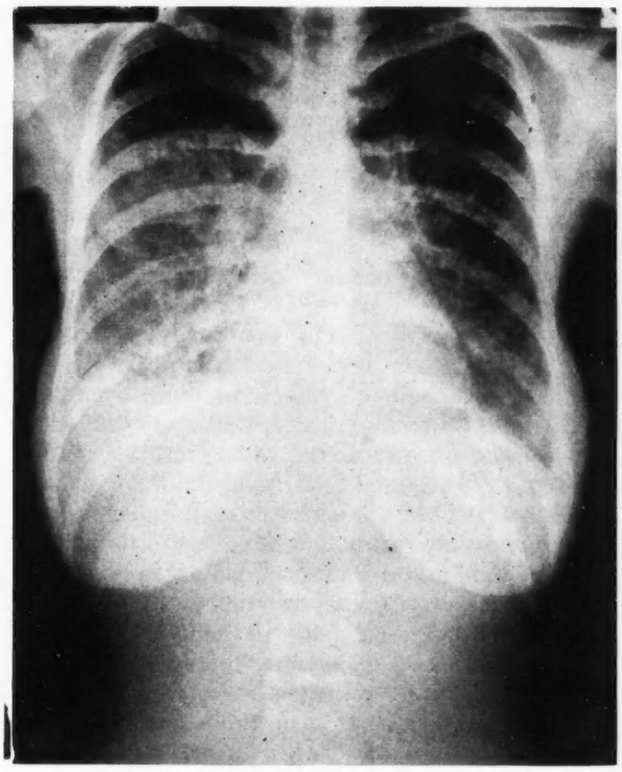

Fig. 1.—Posteroanterior chest radiograph.

ness of the cervix but no other abnormality. The patellar and Achilles' tendon reflexes were absent.

The temperature was 99° F., the pulse 130 per minute, collapsing in type, the respirations 60 per minute and shallow. The blood pressure was 110 mm. Hg systolic and 45 mm. diastolic.

The urine was positive 1+ for protein; the sediment contained rare red blood cells, 30 white blood cells, and rare granular casts, in each high-power field. Examination of the blood revealed a hemoglobin of 10 g. per 100 ml., a hematocrit of 34%, and a white cell count of 41,600 with a shift to the left in the differential leukocyte count. The sedimentation rate was 26 mm./hr. The reticulocyte count was 2.6% and the platelets were normal. The blood urea nitrogen was 36 mg. % and the fasting blood sugar 113 mg. per 100 ml. (Intravenous 5% glucose in water had been given.) The serum sodium was 119, the potassium 5.2, the chloride 80, and the bicarbonate 19 mEq./l. A bone marrow smear was cellular and showed slight hyperactivity of granulopoiesis, compatible with a leukemoid reaction. Radiographic examination of the chest (Fig. 1) showed extensive infiltrative changes throughout both lungs, small bilateral pleural and interlobar effusions, and extensive congestion, presumably lymphatic, termed "B" lines by Kerley. The heart was not enlarged, and no engorgement of the pulmonary vasculature was noted. The electrocardiogram showed sinus tachycardia, and a QR pattern with sharply negative T waves in lead AVL. Multiple blood cultures were sterile, and cultures of sputum, urine, and vaginal smears showed no significant growth.

Following admission, the patient was gravely ill, febrile, dyspneic and exhausted. Intravenous penicillin was started, with the addition of streptomycin, oxygen and digitalis. The pleural effusions increased in size and the patient was in extreme respiratory distress. Death occurred on the third hospital day.

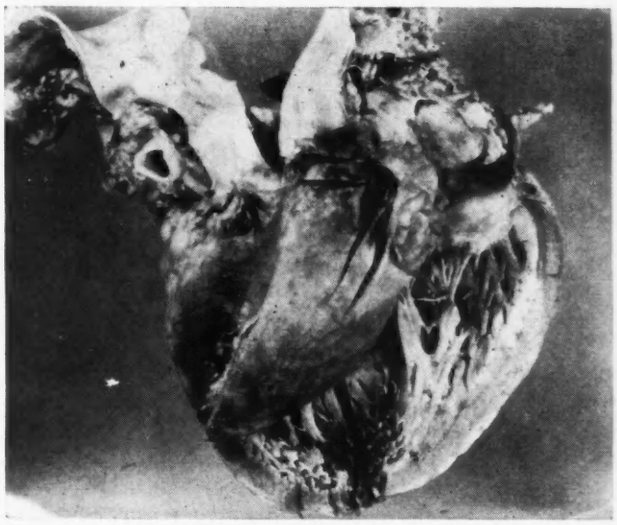

Fig. 2.—The heart opened with lesion incised and showing the area of infarction of the left ventricle.

Autopsy was performed two hours and 15 minutes after death. There was a recent extensive myocardial infarction involving the anterior interventricular septum and the inner half of the anterior and posterolateral wall of the left ventricle. The origin of the circumflex branch of the left coronary artery was obliterated by a necrotic and hemorrhagic cavitating lesion of the ventricular myocardium, approximately 2 cm. in diameter, presenting on the epicardium as a firm reddened area (Figs. 2 and 3) with fistulous

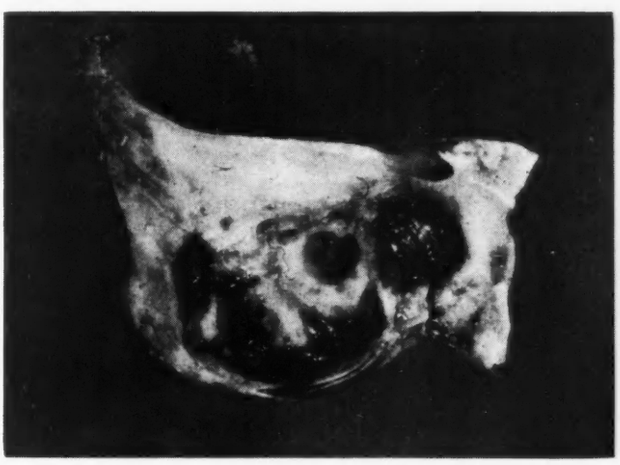

Fig. 3.—Excised tissue block from the cardiac abscess.

communication between the left sinus of Valsalva and the left ventricular cavity beneath the valve leaflet (Fig. 4). The ventricular opening of the fistula was surrounded by a dark red friable mass which projected into the ventricular cavity. All the valve leaflets proper were unremarkable on gross examination, and the right coronary and anterior descending branch of the left coronary artery were entirely normal. No other lesions were present within the heart.

Microscopically, the lesion showed suppuration and hemorrhage with abscess formation (Fig. 5) which involved and partially destroyed the myocardium and epicardium in the region of the origin of the circumflex branch of the left coronary artery. The artery itself was not identified in the sections. The friable mass,

Fig. 4.—The heart: a probe is in the anterior descending branch of the left coronary artery, and wands are in the abscess and the perforations.

projecting into the left ventricular cavity, was composed of thrombus which was organizing at its margins. No bacteria were seen. The base of the aortic valve leaflet adjacent to the lesion was markedly thickened by a deposit of partially organized thrombus.

Grossly, the lungs did not collapse and were edematous. The right lung weighed 520 g., the left 425 g.; the sectioned parenchyma had an unusual yellow-brown colour. Microscopically there was a diffuse generalized "atypical interstitial pneumonitis", with large numbers of deep-staining alveolar macrophages and occasional fibrinoid masses in air spaces.

Additional findings were: bilateral pleural effusions of 1000 c.c. each; ascites 300 c.c.; acute passive congestion of liver, spleen, and kidneys; mild chronic salpingitis; chronic junctional cervicitis with healed erosion. No other site of infection was found.

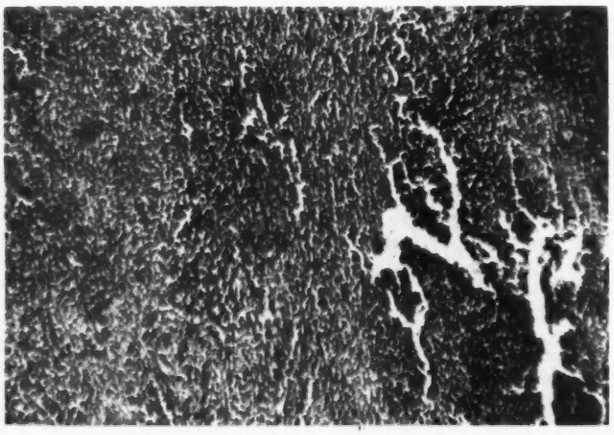

Fig. 5.—Photomicrograph of a portion of the cardiac abscess. (x 100.)

A postmortem blood culture showed no growth, and culture of the abscess content grew only *Strep. fecalis*, which was assumed to be a contaminant.

DISCUSSION

The pathogenesis of the myocardial abscess in this case is obscure. Since previously reported cases have been secondary to septicemia, bacterial endocarditis or a distant focus of suppuration, evidence of these was sought. The extensive pneumonitis was not of a type commonly associated with bacterial infection, and can probably be excluded as a source. Mild chronic salpingitis, presumably the residuum of postpartum infection a year earlier, is an unlikely primary site, especially in view of the paucity of other findings in the pelvis. No antibiotics had been administered in the period prior to admission; thus the numerous negative blood cultures and the lack of appropriate evidence at autopsy tend to rule out septicemia. The fistulous openings into the sinus of Valsalva and left ventricle were possibly the result of ulcerative endocarditis complicated by abscess, but more likely were extensions of the abscess. No aneurysm of the affected coronary artery was found.

Correlation of the clinical history and the pathological findings suggests that coronary occlusion with extensive infarction of the myocardium occurred during the two-week period prior to death. The severe chest pain, dyspnea, cough and sputum are attributable to the ensuing severe congestive heart failure, the pneumonitis, or to both. Since the coronary vessels were normal except in the area of the abscess, it must be assumed that this lesion led directly to the fatal myocardial infarction.

SUMMARY

A 22-year-old woman entered hospital in severe congestive heart failure and died two days later. Unexpected findings at autopsy were extensive myocardial infarction; obliteration of the circumflex branch of the left coronary artery at its origin by a solitary myocardial abscess, the origin of which remains obscure; and an associated acute fistulous bypass of the aortic valve. No similar case could be found in the literature.

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A CASE OF PRIMARY PERITONEAL IMPLANTATION OF AN OVUM

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CONTROVERSY has long raged as to whether *primary* peritoneal implantation of a fertilized ovum is possible, or whether these cases previously reported as primary were in fact secondary to a tubal abortion. It would appear now that there are good grounds for assuming that primary peritoneal nidation is, in fact, a probable occurrence, albeit a rare one.

Galabin[1] in 1896 is credited with presenting the first case of primary peritoneal pregnancy: he operated on a woman who had a 10-week fetus implanted in the pouch of Douglas. The patient died from hemorrhage after removal of the embryo, and an opportunity for examination of the nidation site and pelvic organs was presented at autopsy. The case was submitted to the London Obstetrical Society, who came to the conclusion that it represented a true primary peritoneal pregnancy.

Witthauer[2] reported a case in which he removed a portion of omentum containing a small hematoma which revealed the presence of chorionic villi on microscopic examination; and in 1908, Hirst and Knipe[3] described an embryo of about six weeks' maturity implanted on the posterior aspect of the left broad ligament.

Since then, a number of cases have been reported, purporting to be primary abdominal pregnancies, but many have been of such maturity that the spread of placental tissue has made it difficult to establish the diagnosis beyond doubt. Most of the implantations are described as having occurred in the pelvic peritoneum, but van de Loo[4] reported a case of nidation in the lower border of the liver.

Studdiford[5] presented a case in 1942, which Novak[6] admits to be authentic, in which implantation occurred on the posterior aspect of the uterus; and he has laid down the criteria, which are now most widely accepted, for the diagnosis of primary peritoneal implantation of a fertilized ovum. These are as follows.

1. Both tubes and ovaries must be normal, with no evidence of recent pregnancy or injury.
2. There must be no evidence of a uteroperitoneal fistula.
3. The pregnancy must be related exclusively to the peritoneal surface, and must be young enough to eliminate the possibility of a secondary implantation following primary nidation in the tube.

The case to be reported fulfils these criteria; and represents the youngest, in age of the ovum, which the author has been able to find in the literature.

About noon on March 20, 1961, the author was called to the home of Mrs. D.M., a 23-year-old white, married woman who had had one previous normal pregnancy, delivered in January 1960. She complained of having suffered an acute attack of lower abdominal pain five days previously, localized mainly in the rectum, which had lasted about 20 minutes and then subsided. A similar attack had occurred the following day, March 16; then she had been symptom-free until that morning, during which the pain had been occurring intermittently. The patient volunteered the information that she must be pregnant, for she was two days overdue with her menstruation. Her menses were so regular apparently, every 28 days, that even in the absence of any of the appropriate symptoms she was convinced that she must be pregnant. She was not then in much distress, but there was vague lower abdominal tenderness. The cervix was firm; the uterus small and anteverted; the ovaries and tubes could be palpated at that time and seemed normal, but rectal examination, though otherwise negative, was extremely painful, as was any attempt to move the cervix.

She was admitted to the Langenburg Union Hospital for observation. Her hemoglobin was found to be 12.0 g. %, and her leukocyte count 20,000 per c.mm. Over the next three hours, the abdominal pain grew steadily more severe; her pulse rate rose and her blood pressure fell; she became weak and faint, and complained of "fullness" of the abdomen and ultimately of pain in the shoulders and difficulty in breathing. By this time, because she presented a classical picture of massive intraperitoneal hemorrhage, laparotomy was undertaken during which blood transfusions for replacement were given.

On opening the abdomen, the peritoneal cavity was full of blood, with a few blood clots in the pelvis. The uterus, tubes and ovaries were carefully examined but seemed perfectly normal. The source of the bleeding was finally located, in the depths of the pouch of Douglas, where a small triangular tear in the peritoneum covering the anterior aspect of the rectum was found. This was no greater than 1 in. (2.5 cm.) in length but was oozing steadily. Protruding through the laceration was a tiny piece of purplish-black tissue which was removed for histological examination. There were no signs of ectopic endometrial tissue in any other location within the abdomen. Bleeding was controlled by oversewing the laceration, the peritoneal cavity was cleared of blood and clots, and the abdomen closed; the patient made an uneventful recovery. The pathological report on the biopsy specimen reads as follows: "Sections show fragments of hemorrhagic membranous tissue which in some areas have the appearance of decidual tissue. Also present are numerous clusters of trophoblastic cells, and two chorionic villi are seen. The appearances are consistent with the clinical diagnosis of a ruptured ectopic pregnancy."

SUMMARY

A brief, partial review of the earlier literature on primary abdominal pregnancy is presented, and the criteria for the diagnosis are re-stated.

A case is reported of primary implanted pregnancy on the peritoneal surface of the rectum.

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SOME REFLECTIONS ON GENIUS[1]

THOSE who have read his other books will not be surprised to find that the President of the Royal College of Physicians of London writes well. Indeed, his latest book puts him among the better essayists of our day. One is only sorry that there is not more of his pithy, learned and very readable writing in this thin volume. Yet the book is nearly 200 pages in length and it must be the quality of these essays which makes one hope for more, and watch the end of the book approaching with discomfort. This in itself is a hallmark of the successful essayist and shows how Sir Russell Brain has mastered this tricky medium of expression. Anyone who tries his hand at it knows just how hard it is to get the right blend of form and content which is necessary to produce a successful essay.

Medical essays are peculiarly difficult. They must be technically sound. The content must be appropriate to the essay form, and then one begins. It is not enough to know one's subject or even to write adequately. One must be able to do all this with an illuminating compression which evokes in even the most sophisticated reader an "Aha—I'd never thought of it quite that way." If such a reader is even mildly compulsive, he is driven to underline and annotate, which may be vexing for other compulsive readers of the same book, but shows that it has gripped one. This is an underlinable book.

There are 14 essays in this book including the title piece, which is one of the best on this subject—Genius. Six essays concern one of the greatest non-medical doctors, Samuel Johnson, and they should be read by any lover of the great lexicographer. I think that Sir Russell writes better than Osler, but then this may simply be that his style has that tautness and muscularity which we esteem more now than Osler's studied smoothness. His writing certainly measures up to that of Wilfred Trotter,[2] and this is higher praise than one can often give. Trotter's essays remain extraordinary efforts of clarity and brilliance and there has been little better writing on the relationship between medicine and science. Sir Russell's range is wide. He goes from Grock to Swift via Epstein and Christopher Smart. The title essay sets the pace. His reflections on genius are wise, thoughtful and humane. He discusses intelligence tests subtly—"Without going into the question of what is being tested by intelligence tests, and whether the function being explored is single or multiple, there can be no doubt that it is a function or group of functions of a highly special kind. The schemas are those concerned in conceptual or abstract thought. This is of the essence of some kinds of genius but by no means all. Consider the different parts played by intelligence in the philosopher, in whose work conceptual thought turns round and reflects on itself, the scientist who directs it upon the data of observation, and the artist in whom its role is altogether more obscure and intimately related to feeling."

In recent scientific writings on creativity there is a tendency to neglect poetic inspiration. Sir Russell puts it in its proper place—"The ordinary man has been prone to dismiss poetic inspiration as a harmless form of madness of no interest except to the few eccentrics who enjoy poetry, but the geniuses of science recognize that the inspiration which leads to scientific discovery does not differ from that of the poet in its nature, but only in its subject matter." Here for instance is an account of Sir William Bragg,[3] the crystallographer, wrestling with the problem. "The analyst has before him the separate bits of a jigsaw puzzle and he has to fit them together . . . in making guesses at possible arrangements he draws on a wealth of experience . . . I can well remember the intense concentration. One lived with the structure. I'm tempted to say one ate, slept and shaved with it. Finally, after six months or longer, and if one were fortunate, everything suddenly clicked into place. . . ." This differs very little from many accounts of a poet or composer developing their ideas. I have been able to watch an inventor of genius who works in that uncertain territory where chemistry, physiology and electronics jostle each other. If he is pressed to say just why he does this or that, he can only reply "I feel that it will work." So far as I can make out, the course of discovery goes something like this. First come obscure feelings very hard to put into words that something is going to happen. This is accompanied by a questing excitement such as a terrier shows when he smells a rat. This grows and becomes what seems to an outsider a frenzy of muddled and crude experiments which can be continued for hours or even days at a time. Through these experiments his ideas gradually become clearer and so are, haltingly at first, put into words. The words are rarely very impressive at the start, but those who

know my friend respect him and have learnt from experience that he is hunting something. Talking with friends transmits and amplifies the excitement and so generates new ideas and experiments which become more and more precise. I have watched this happen several times and it always seems to go in much the same way.

Sir Russell does not ignore administrative genius, and in this he is of course in the Greek tradition, for they rated it very highly. He writes: "The genius in these fields must possess an outstanding intelligence which operates on the minds of men as well as on their material circumstances. As with the artist, however, it is a special blend of feeling with thought that enables his cerebral schemas to reflect the thoughts and feelings of his fellows and to modify the pattern of events by discerning in them meaning that eludes the less gifted. But his task is far harder than that of the novelist or the playwright, for he must take his characters as he finds them and by his superior knowledge and will impose his plot on theirs. He is the artist in action." A President of the Royal College of Physicians of London has opportunity enough to "meddle with the governing of men" so that he can recognize it as being an art as difficult as it is fascinating. Like another great essayist, Sir Russell has combined thought and action in his life so that his reflections on either are ripe, and as Dr. Johnson once said of brandy "fit for heroes".

HUMPHREY OSMOND

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PREDIABETES IN MOTHERS OF LARGE INFANTS

WOMEN who subsequently develop diabetes mellitus often have abnormally large infants, and the perinatal mortality among their children is high, perhaps even higher than that among children of women with well-controlled frank diabetes. In some women who have had an abnormally large child or whose infant was stillborn or died neonatally, an oral glucose tolerance test performed in a subsequent pregnancy is found to be of the diabetic type. In the majority of such cases, the glucose tolerance test reverts to normal in the puerperium.

In many women, therefore, the glucose tolerance test will fail to detect a tendency to diabetes. It was because of the need for a test that would detect impairment of the reserve capacity of the pancreatic islets that Fajans and Conn[1] introduced their "cortisone-stressed glucose tolerance test". More recently Joplin, Frazer and Keeley[2] have evolved an alternative test based on the quantitative measurement of the overnight glycosuria after administering 60 mg. of prednisone.

After three days on a controlled diet, and after simple preliminary blood and urine glucose estimations, three 20-mg. doses of prednisone are given at mid-day, 4 p.m. and 8 p.m., and the urine passed between 10 p.m. and 6 a.m. the following day is collected from the fasting subject. The overnight urinary glucose output is measured by a simple titration method; over 60 mg. per hour is abnormal. Where possible, blood is also taken at midnight and 1 a.m. for sugar estimation; over 133 mg. per 100 ml. is considered to be abnormal.

Davey, Joplin and Santander[3] have recently reported the results of studies in which they performed the prednisone-glycosuria test on 10 men and normal non-pregnant women, on 11 normal pregnant women, and on 13 mothers of large infants over 9 lb. In all of these subjects the glucose tolerance test gave normal results. The rate of urinary excretion of glucose after prednisone administration to the normal pregnant women did not differ significantly from that in the normal men and non-pregnant women. Taking the upper limit of normal for the rate of overnight glycosuria after prednisone as 60 mg. of "titration" glucose per hour, nine of the 13 mothers of large infants responded abnormally to prednisone.

It is reasonable to suppose that patients who have an abnormal prednisone-glycosuria test have some impairment of pancreatic function which, if it progresses, will result in overt diabetes. Such an early stage of this disease, at which levels of blood and urine sugar are still normal, has been aptly termed "prediabetes". Women with abnormal prednisone-glycosuria tests may thus provisionally be regarded as prediabetic. When later, though the patient is still clinically well, the standard oral glucose tolerance test has become clearly abnormal, the condition is best described as "subclinical diabetes".

Recent studies suggest that carbohydrate restriction and/or insulin therapy, together with induction of premature labour, can significantly reduce the perinatal mortality in infants of women with subclinical diabetes. The place of these measures in the management of pregnancy in the prediabetic and latent diabetic woman has yet to be evaluated. If it is shown that the infants of women who have an abnormal prednisone-glycosuria test have an increased perinatal mortality, and that carbohydrate restriction, insulin, or induction of premature labour significantly reduces this mortality, then a test for prediabetes, such as the prednisone-glycosuria test, may well have an important place in obstetrics.

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SUPPORT OF GROWTH HORMONE RESEARCH

SINCE it was organized in 1956, the Growth Hormone Allocation Committee of the Canadian Society for Clinical Investigation has been charged with the responsibility of procuring sufficient amounts of this hormone to supply the needs of Canadian investigators in this field. The Committee is made up of Dr. D. R. Wilson of Edmonton, Dr. A. L. Chute of Toronto, Mr. Kell Antoft of Montreal and Dr. J. C. Beck of Montreal as chairman. The activities of the Committee arise out of its primary responsibility of allocating the limited supply of human growth hormone to a few carefully selected research projects. The need of an organization to supply human pituitary glands, and to supervise the distribution of the small amounts of rare and precious hormone subsequently extracted from them, was recognized by the Society at an early date. Canadian workers in this important field are cognizant of the advantages accruing from this arrangement, in comparison to the "catch-as-catch-can" atmosphere that exists elsewhere. In other countries where there is no such central collecting agency, each research group must, perforce, scramble for the available supply of pituitary glands. In addition, outside Canada there is no central clearing house for the exchange of information on current research activities, so that waste and duplication inevitably occur.

In Canada, under present arrangements, the departments of pathology of university and other major hospitals supply the pituitary glands, obtained during routine autopsies, to the Committee without charge. The growth and adrenocorticotropic hormones are extracted (at the manufacturer's expense) through collaboration with a Canadian pharmaceutical company, Nordic Biochemicals Ltd. Although the original procedures for the manufacture of growth hormone were developed by Rabens, workers at Nordic have originated a number of technical advances in this field. They will underwrite shipping and handling charges and will advise regarding the method of storing the tissue prior to shipping, and other details (see below). This company supplies the hormones so obtained, free of charge, to those investigators whose projects have been approved by the Growth Hormone Allocation Committee.

The past success of this project has depended upon the co-operation of the pathologists, residents in pathology and laboratory technicians of many Canadian hospitals, and it is important that these personnel be encouraged to continue and, if possible, to increase their contributions to this program. In addition, many more pathologists and their non-medical staffs might be approached, through whatever channels are deemed necessary after consultation with the Canadian Association of Pathologists, in order that they also may contribute to this important effort.

The species specificity of growth hormone is decisive; only human growth hormone is effective in human patients. Currently a number of very important investigations are under way to unravel the physiological significance of growth hormone. Apart from the obvious need for long-term investigations in the treatment of panhypopituitary dwarfism, work is being carried on to develop an immunological assay method sensitive enough to measure blood levels of growth hormone and also to determine the effect of growth hormone in conditions such as diabetes and impaired renal function. A number of other studies appear worthy of further investigation and should be carried out if and when additional supplies of the hormone become available. As an indication of the work made possible through the activities of this Committee, the success of Beck and his co-workers at the Royal Victoria Hospital, Montreal, in demonstrating the species specificity of growth hormone in humans, in 1957, is a distinguished Canadian contribution to this field.

TECHNIQUES FOR COLLECTION OF HUMAN PITUITARIES FOR GROWTH HORMONE EXTRACTION

As growth hormone activity seems to be fairly stable, the time interval between death and removal of the gland does not seem to be of any real importance and the pituitaries may be removed at any time within 48 hours of death.

After removal, the tissue should be placed in a litre flask containing cold acetone. The flask should be stored in the refrigerator. Whenever new pituitaries are placed in the flask, it should be gently agitated so that the extracted water is dispersed throughout the acetone.

After pituitaries have been collected in the flask for a week, they should be allowed to stand for a further three to four days without adding further pituitaries. Then the old acetone should be discarded, the pituitaries allowed to drain, and fresh acetone added.

In the second acetone change, the pituitaries may be stored until enough have been collected for shipment. Two days before shipment, they should be removed from the acetone for 24 hours and allowed to dry in room air. They may then be mailed in the desiccated state in any suitable container.

Pituitaries from all types of cases are acceptable, except where the disease process has involved the pituitary itself. Thus, pituitaries which exhibit neoplastic involvement are best excluded.

If a large supply of infant and children pituitaries is accumulated, they should be kept separate from the adult pituitaries for comparative purposes.

Sectioning of the pituitaries for histological examination does not interfere with the activity of growth hormone, providing the cut remains of the pituitary are immediately placed in acetone.

CHANGE OF ADDRESS

Subscribers should notify the Canadian Medical Association of their change of address one month before the date on which it becomes effective, in order that they may receive the Journal without interruption. The coupon on page 31 is for your convenience.

Letters to the Journal

CONTROLLED DRUGS

To the Editor:

In the editorial note on Controlled Drugs which I contributed to the issue of September 9 (*Canad. M. A. J.*, 85: 661, 1961), I find that I have overstated the case for written prescriptions for the amphetamines and the barbiturates.

Pharmacists may dispense Controlled Drugs on the strength of a prescription given verbally by a physician as well as by a prescription in writing. The pharmacist must record the verbal prescription at once and retain the record of the transaction for future reference. The same conditions apply to supplies of Controlled Drugs obtained by doctors from pharmacists for use in their practices. A prescription which requires to be refilled must be written and must indicate clearly the number of times and the dates that it may be refilled.

It is of interest that the new regulations respecting Controlled Drugs will be administered and enforced by the Narcotic Control Division of the Food and Drug Directorate.

A. D. KELLY,
General Secretary

FATALITIES FROM OVERDOSAGE OF ANTIDEPRESSANT DRUGS

To the Editor:

I was pleased to note the publication in your August 12, 1961, issue of Dr. Babiak's case report of a fatality from an overdose of antidepressant drugs (*Canad. M. A. J.*, 85: 377, 1961). It has prompted me to mention briefly observations on similar cases from the Toronto East General Hospital in 1960-61.

There were in this period three deaths from these drugs. The first was a young child who died following ingestion of imipramine (Tofranil). The second was a successful suicidal attempt of a middle-aged woman from taking an unknown quantity of tranylcypromine—trifluoperazine (Parstelin).

The third patient was a young man in the third decade who had a previous history of two suicidal attempts. Because of our prior experience, this man was treated quickly and intensively. He was first seen within one hour of taking an unknown number of aspirin tablets and approximately 40 Parstelin (tranylcypromine—trifluoperazine) tablets. Physical examination was then normal and gastric lavage was immediately done, but in the next one-half hour he became increasingly drowsy and disoriented and this was followed by a grand mal seizure which persisted until his death 45 minutes from its start. The seizure was chiefly in the tonic phase except for the face, which underwent twitching and contortions of the extrapyramidal type. Treatment with two doses each of I.M. paraldehyde, I.M. phenobarbital (Luminal), I.V. benztropine (Cogentin) and I.V. diphenylhydantoin (Sodium Dilantin) was unsuccessful. Autopsy on the two deaths from tranylcypromine—trifluoperazine (Parstelin) showed only mild cerebral hyperemia. It was possible that severe hyperpyrexia, presumably due to the seizure, contributed to the cause of death.

It was felt that the only hope in future cases lay in the use of general anesthesia and curare. One striking observation is that of the many more cases of barbiturate overdose in that year, one of whom was unconscious for five days, none died. Very little literature is available on the occurrence and treatment of these cases, and it is hoped that this letter will herald its appearance.

C. R. BATEMAN, M.D.

42 Albert St.,
Stratford, Ont.

HEALTH HAZARDS IN SMOKING

To the Editor:

Will organized medicine be the last to recognize the health hazards in smoking? Is it not time that the profession have the opinion of its parent body concerning this vital subject? A physician who smokes should be able to say "I smoke but I cannot help it. The medical profession does recognize, however, that tobacco smoking is a serious health hazard, particularly because of the element of addiction to tobacco, etc."

Individuals within the profession continue to warn of the need of such a stand. The last such concludes his article (*Canad. M. A. J.*, 84: 1374, 1961) with the remarks: "The relationship between lung cancer and cigarette smoking appears inescapable. The facts warrant presentation to the public without the contradictory claims heretofore apparent. The medical profession must no longer fail to accept responsibility in this regard."

CARL J. REICH, M.D.

Suite 202,
624-6th Street, New Westminster, B.C.

LIVE ORAL POLIOVIRUS VACCINE AFTER DPT POLIO VACCINE

To the Editor:

In their article in the Journal of September 2, (*Canad. M. A. J.*, 85: 575, 1961) Dr. Wilt and coauthors state that, because of occasional untoward reactions from DPTP vaccine in children over six years of age . . ., the use of DTP (diphtheria, tetanus, poliomyelitis) vaccine is recommended for children over six years of age.

It should be noted, however, that DTP vaccine is recommended for reinforcing doses only in children and adolescents of school age who have previously been immunized against diphtheria, tetanus and poliomyelitis in infancy and preschool years.

This preparation contains 10 Lf of diphtheria toxoid, which is not enough to act as a primary immunizing agent against diphtheria.

S. P. C. CASEY, M.B., D.P.H.,
Medical Officer of Health

Wetoka Health Unit,
Wetaskiwin, Alta.

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MEDICAL NEWS IN BRIEF

STRESS INCONTINENCE

A study of the onset of stress incontinence in a random sample of 400 pregnant women has recently been reported from Britain by Francis (*Brit. M. J.*, 1: 1747, 1961). Of these women 268, or 67%, admitted to some degree of stress incontinence during the current pregnancy—53% of the 222 primigravidae and 85% of the 178 multigravidae. The outstanding conclusion reached from this research, and from experience in following the 400 women through labour and the puerperium, was that stress incontinence rarely if ever appeared for the first time after childbirth. The symptom either began before the first pregnancy or during the first or a subsequent pregnancy, and every woman who had stress incontinence in the puerperium had suffered from it during the preceding gestation. Once manifested, the disability generally increased in degree in successive pregnancies and might then persist in the absence of pregnancies. The characteristic radiographic sign of loss of the posterior urethrovesical angle was seen in 30 of the 33 women with incontinence, but only in 4 of 50 women with good control of the bladder. Follow-up of these women, and of others afflicted by stress incontinence during pregnancy, showed that within a few days of delivery nine out of ten women previously troubled regained good control of the bladder, even though radiographs showed no restoration of the lost angle; that is, functional cure preceded anatomical return to normal. This investigation has produced valuable evidence that women do not develop stress incontinence because of the strains of labour, but that those who suffer from this discomfort in later life are destined from an early age to do so, and that pregnancy, not labour, commonly reveals or exaggerates an intrinsic defect in their sphincter mechanism.

SWEAT ELECTROLYTE CONCENTRATION IN CYSTIC FIBROSIS, ADDISON'S DISEASE AND PITUITARY DWARFISM

The method described by Gibson and Cooke for obtaining sweat samples through pilocarpine iontophoresis has been in use at the Pediatric Clinic of Zurich (Professor Fanconi) since 1959.

Fanconi (*Schweiz. med. Wchnschr.*, 91: 578, 1961) describes the technique and states that usually 70 to 300 mg. of sweat can be obtained from any one area, and sometimes the yield has been as high as 500 mg. The average normal electrolyte content of sweat was found to be 12.5 mEq./l. for sodium, 10.8 mEq./l. for chloride, and 10.7 mEq./l. for potassium (with the values swinging from the extreme low of 2 to the extreme high of 30 mEq./l.). In 24 patients aged 4 weeks to 15¼ years, of whom 8 were boys and 16 girls, all suffering from cystic fibrosis of the pancreas, the average concentrations were: Na 83.3 mEq./l., Cl 92.9 mEq./l., and K 21.7 mEq./l. These values were almost seven times higher than normal for sodium, nine times higher than normal for chloride and twice normal for potassium. In the parents of these children some elevation of electrolytes in the sweat was found, but the values never reached such excessively high levels as those of the children. The normal siblings of the patients failed to show any marked abnormality of their sweat.

In a 14½-year-old boy with untreated Addison's disease, the salt concentration in the sweat was, as expected, very high. Whilst cortisone alone did not reduce this excessive excretion of salt in the sweat, an injection of desoxycorticosterone acetate in oil (Percorten) brought about complete normalization of the salt content of the sweat. Thus the concentration of electrolytes in sweat could be used as a criterion in adjusting the therapy of patients with Addison's disease.

Abnormalities of sodium and chloride content were found in some of the cases of pituitary insufficiency due to hypophysectomy and in six of 11 cases of pituitary dwarfism.

No explanation could be found for the variable electrolyte content of sweat in the other cases.

A LOCAL OUTBREAK OF TRICHINOSIS

Although the incidence of trichinosis is declining, it is not yet eliminated from the United States or Canada, and it continues to be a menace to the public health, because pigs—in certain cases—are fed with household garbage and because natural reservoirs of the parasite persist in rodents. In certain areas trichinosis is most common in people of German or Italian ancestry, i.e. in populations who eat crude pork products. A recent paper by Shields (*Ann. Int. Med.*, 54: 734, 1961) describes an outbreak of trichinosis in a rural community. The commonest symptoms were headache, malaise, fever, chills, weakness, myalgia and periorbital edema. Abdominal cramps were common. Prolonged episodes of diarrhea and involvement of the peripheral nerves were among the less usual manifestations. Residual edema of the legs and periorbital tissue persisted as long as six months after the onset of symptoms in certain cases.

Laboratory methods of diagnosis are discussed. The greatest degree of eosinophilia varied between 25 and 53%, but fell to normal in all the patients at the end of six months. The bentonite flocculation test was more useful in the diagnosis than the complement fixation test, but a positive titre was not found in any of the unproved or only suspected cases.

The epidemiologic investigations showed that the source of the outbreak was fresh sausage, made locally from numerous pork carcasses, originating in four packing houses with state licences. In seven patients the presence of trichinosis was proved, and six of these admitted that they had eaten raw sausage. The investigation of these cases resulted in a suspicion of trichinosis in 10 other subjects, principally members of the families of the hospitalized patients. The factor of dilution in the preparation of sausages makes it probable that many other individuals in the community had subclinical infestations.

(Continued on advertising page 16)

OBITUARIES

DR. MURRAY SCOTT DOUGLAS, 62, past Chairman of the General Council and the Executive Committee of the Canadian Medical Association, died at the Toronto General Hospital on August 28. Dr. Douglas was born in London, Ont., and received his early education from the London Collegiate Institute. In 1922 he graduated from the University of Western Ontario Medical School. During the last two years of his medical studies he interned at the Victoria Hospital, London, Ont.

Artona, Windsor

Dr. Murray Scott Douglas

As a general practitioner, he practised first in Smooth Rock Falls and Kapuskasing, Ont., from 1922 to 1924, and then in Windsor, Ont. From 1953 he limited his practice to obstetrics and gynecology. During the Second World War he served in the R.C.A.M.C., with the rank of Captain.

Dr. Douglas was very active in both medical and lay circles, and was a member of many boards, committees, and other organizations. The most notable of these are: the Canadian Medical Association as a member of the Executive Committee for three years prior to becoming Chairman; the Ontario Medical Association, of which he was a president; the Metropolitan General Hospital, Windsor, which he served as Chief of the Department of Obstetrics and Gynecology, as a member of the Board of Governors, as a member of the Medical Executive, and as president of the hospital staff; the Western Ontario Society of Obstetricians and Gynecologists, of which he was a founding member and a president; the Essex County Medical Society, which he served as president, treasurer, and executive member; the Wayne County Medical Society; Windsor Medical Services, of which he was secretary-treasurer and one of the first directors; the Windsor Club, of which he was a president; the Windsor Chamber of Commerce; and the Student Aid Foundation of Essex County, of which he was a director.

He is survived by his widow and two sons.

DR. MURRAY SCOTT DOUGLAS

An Appreciation

The sudden death of Dr. Murray S. Douglas has come as a blow to the medical profession of Canada. This energetic and kindly man has left his mark on Canadian medicine, not only in his home city of Windsor but also in the broader field of the Canadian Medical Association.

Dr. Douglas graduated from the University of Western Ontario in 1922 and, like many other young doctors of that time, began his professional career in the northern part of the province of Ontario. He practised for two years in Smooth Rock Falls and Kapuskasing. The experiences gained during those years were often recounted and gave Dr. Douglas an appreciation of the difficulties encountered in medical practice outside the larger centres of population.

In 1924 Dr. Douglas moved to the city of Windsor, where he soon established a large general practice. Like many others, he found himself living through the depression of the thirties, and these experiences so impressed him that he became instrumental, along with other Windsor doctors, in establishing Windsor Medical Services—an organization originally designed to bring patient and doctor together, so that people might with foresight and dignity prepay the cost of illness. Dr. Douglas served as the first Secretary-Treasurer and was one of the first members of the Board of Directors of Windsor Medical Services. His faith in this organization never wavered and he had the opportunity to see that faith fulfilled.

During succeeding years Dr. Douglas became Treasurer of the Essex County Medical Society and in 1952 became its President. His confrères in Windsor, recognizing his abilities in the field of medical organization, encouraged him to lend his talents to a broader field, and he became a District Councillor and member of the Board of Directors of the Ontario Medical Association. In 1957 he was honoured by the medical profession of Ontario by being elected President of the Ontario Medical Association.

During these years of activity in the provincial medical association he never failed or neglected his obligations to his profession in his own city. He served as President of the Metropolitan General staff and for fifteen years acted as Chief of the Department of Obstetrics and Gynecology of that hospital. He was a founding member and President of the Windsor Obstetricians and Gynaecologists Travel Club, and a founding member and President of the Western Ontario Society of Obstetricians and Gynaecologists. Dr. Douglas was also active in civic affairs and served on the Board of Directors of Goodwill Industries of Wind-

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sor, an organization designed to assist handicapped persons.

The Essex County Medical Society in 1957 made Dr. Douglas a Life Member in recognition of his services to medicine in Windsor.

In 1959 the Canadian Medical Association, recognizing Dr. Douglas's abilities and keen interest in organized medicine, elected him Chairman of General Council, a post he held until his retirement in June of 1961. Also in 1959 he was one of the representatives of the Canadian Medical Association to the meeting of the British Medical Association in London, England, on the occasion of the election and installation of His Royal Highness The Prince Philip, Duke of Edinburgh, as President of the British Medical Association.

To all these activities and others too numerous to recount, Dr. Douglas gave unstintingly of his time and his energy, sometimes to the point of physical exhaustion. He was never too busy to listen to the thoughts of his confrères on medical matters, and never so fixed in his thinking that advice and ideas of others did not receive careful and sympathetic consideration.

By those of us who were fortunate enough to be counted among his friends he will be remembered not only for his contributions to medicine but for his kindly personality. As a host he had no superior. He never indulged in idle gossip, and if he could not say a kind word he held his counsel. With the perpetually fresh rose in his buttonhole and his outgoing and friendly smile, he presented at all times the personality which was the true Murray Douglas, "a man who loved his fellowmen". To no one could more aptly be applied the statement that "the measure of a man's life is not its duration, but its donation".

To his widow, Edith, and their sons Robert and David goes the sympathy of the medical profession of Canada. E.K.L.

DR. ARTHUR LYON

AN APPRECIATION

Dr. Arthur Lyon, born in Huron County, Ont., on April 16, 1910, died in Windsor on July 11, 1961.

After graduation from Clinton Collegiate Institute, he attended the Toronto Normal School. He acted as assistant principal of King Edward School, Kitchener, for four years, after which he entered the University of Toronto, graduating in medicine in 1939. He served as an intern in the Metropolitan General Hospital, Windsor, for the summer of 1938, and in St. Michael's, Toronto, 1939-1940, before entering upon the practice of medicine in Windsor in association with Dr. Neil MacDonald in 1940.

Dr. Lyon was a member of the Essex County Medical Society, and its President in 1954. He took an active part as Director in Windsor Medical Services and later with Trans-Canada Medical Plans, of which organization he was Chairman in 1959-1960. He was a member of the Ontario Medical and Canadian Medical Associations, and associated with staffs of all the local hospitals.

Dr. Lyon was a member of St. Andrew's Presbyterian Church, the Essex Golf and Country Club, and also was active in the Lions Club.

His unexpected death at the height of his activities has removed from the medical profession one whose whole life was dedicated to the service of humanity. He will long be remembered for his friendliness, integrity and sense of good humour. He is survived by his widow, the former Miss Ruth Schmitt; two sons, Arthur and W. Kirk, at home; his mother, Mrs. Wm. Lyon, Londesboro; one brother, Dr. E. Kirk Lyon, Leamington; and two sisters, Mrs. John (Marjorie) Moroso, Hamilton, and Mrs. Ruth Meyers, Simcoe. To these, members of Essex County Medical Society and friends extend deepest sympathy. J.W.B.

DR. ARCHIBALD KITCHENER McNEILL, 61, died at his home in Empress, Alta., on August 2. Born in Asquith, Sask., he attended the University of Saskatchewan in Saskatoon, and graduated from the Manitoba Medical School in 1926.

Dr. McNeill was a past master of the Masonic Lodge in Empress.

He is survived by his widow, three daughters and two sisters.

DR. ROBERT WESLEY SHAW, 92, died August 1 at his home in London, Ont. A former chairman of the London board of education, he was also a member of the board of control in 1917 and a member of the London Railway Commission in 1919-20.

Born near Mitchell, Ont., Dr. Shaw graduated from Western Medical College, and University College, London, England. He was a member of the London Royal College of Physicians, London, and a member of the Royal College of Surgeons.

Dr. Shaw is survived by one daughter.

DR. GEORGE T. WILSON

AN APPRECIATION

New Westminster, B.C., has a long and honourable medical history, and we look back on a long list of men from that community who have made their mark in medicine, and contributed to the progress of their profession — John M. Walker, Manchester, the McEwen brothers, Cannon, Bill Clarke, R. Crease, and many others come to mind.

One of them, and by no means the least, was Dr. George T. Wilson, who for many years practised in New Westminster, first as a general practitioner and later as a specialist in surgery. A native of New Westminster, he graduated from McGill University Medical School in 1910. He enlisted with the C.A.M.C. in the Cavalry Division during World War I. He has been Chief of Staff of the Royal Columbian Hospital and past president of the Fraser Valley Medical Association, and has been very active in medical politics. He was the recipient of Life Membership in the College of Physicians and Surgeons.

George Wilson fulfilled his duty, and more besides, to his profession, and to his practice of that profession. He was a quiet, unassuming man; charming and courteous in manner, and a good man to know. The medical profession of British Columbia is the poorer for his loss.

He died on July 7, while on a fishing trip, and his end was a happy one. We who knew him and valued his friendship will be glad of that.

To his widow and family we extend our sympathy and condolences. J.H.MACD.

BOOK REVIEWS

HYPERTENSION—CHEMICAL AND HORMONAL FACTORS. Volume IX. Proceedings of the Council for High Blood Pressure Research, American Heart Association, November 1960. Edited by Floyd R. Skelton. 806 pp. American Heart Association, Inc., New York, 1961. $2.50.

This volume consists of nine articles which analyze the problem of hypertension in terms of the possible roles of the autonomic nervous system, various pressor amines, renal pressor hormones, adrenal cortical secretion of aldosterone and the state of reactivity of the blood vessels themselves.

Although some of the articles are highly technical, the style is generally fluid, the ideas are clear and many of the experiments and theories are brilliant and fascinating.

Since the problem of hypertension cuts across all medical specialties, this volume is recommended for all physicians, but it is particularly called to the attention of internists and physicians interested in the problem of hypertension.

The metabolism and degeneration of the catecholamines and the role therein of various enzymes is excellently summarized.

Other interesting chapters describe the unusual reactivity of the arterioles of hypertensive patients, the more effective diagnosis of pheochromocytoma, and the probable relationship between the renal pressor system —angiotensin II and aldosterone secretion by the adrenal cortex as well as its possible relationship to sodium.

Although a review of this volume can lead to no final conclusion regarding the etiology of hypertension, one is left with the impression that the study of hypertension has become a highly dynamic one, and that many of the findings described herein may lead us shortly to a much clearer understanding of the etiology of hypertension and hence to more effective therapy.

ADVANCES IN THYROID RESEARCH. Transactions of the Fourth International Goitre Conference, London, July 1960. Edited by Rosalind Pitt-Rivers. 529 pp. Illust. Pergamon Press Ltd., Oxford; Pergamon Press, Inc., New York, 1961. $20.00.

This book comprises a compendium of the papers presented at the Fourth International Goitre Conference in London, England, July 1960. Addresses by Sir Charles Harrington, President of the Conference, and by the late Dr. Ramsdell, then President of the American Goiter Association, are included as forewords; these two addresses stressed the remarkable changes in thyroid research that have occurred since the Third International Conference in 1938. Although new tools and techniques have contributed materially to this expansion of information, the widening fundamental approach stimulated by the intellectual dissatisfaction regarding the gaps in our knowledge has been of perhaps greater importance. It is indeed evident from the papers which comprise the book that this fundamental approach is of ever more importance, although purely clinical papers are by no means lacking. Nevertheless, the "team" approach to research (in this case, thyroid gland research) with biochemists and other basic scientists as full team members along with physicians, is very well demonstrated by numerous excellent presentations, and appears to be the most productive and efficient type of research combination.

Since the original texts of presentations have been adhered to as much as possible, the papers are short, easily read and easily understood. The type and illustrations are clearly printed. A wide diversity is apparent in the subject matter of the 94 papers which were presented by thyroidologists from 28 countries. Such currently important topics as antithyroid antibodies, thyroxine binding globulin, the thyroid "activator" in hyperthyroidism, TSH assays, and intrathyroidal metabolic abnormalities are covered in numerous articles, as are a host of other topics related to surgical, medical or fundamental aspects of thyroid gland investigation.

Since the papers collectively represent the frontier of thyroid research, the book will appeal primarily to those physicians and investigators who have a major interest in the function of the thyroid gland. To such readers, the book will prove very useful and informative; it will, however, have less appeal for the more general medical reader, although he may find many of the facets covered of considerable clinical interest.

QUANTITATIVE CELLULAR HAEMATOLOGY. American Lecture Series. J. M. Yoffey. 122 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $6.00.

Quantitative studies on bone marrow and techniques for measuring its cell output are clearly outlined. The author demonstrates quite nicely the advantages of quantitative studies over qualitative methods, and in his conclusions contrasts the large myeloid reserve with the low reserve of erythropoietic cells.

Once again the origin of the bone marrow lymphocyte is discussed. Its mode of production in the lymph node and its rate of formation, distribution and circulation are described.

Histological studies of lymphoid tissues and estimates of desoxyribonucleic acid (DNA) turnover are in full accord with the concept of extensive new cell formation and re-circulation.

Whether the bone marrow lymphocyte is hematogenous in origin or not is uncertain, but at least its role and importance as a stem cell, once in the normal adult bone marrow, are established.

The hematopoietic system emerges as a source of active cell proliferation in the bone marrow, lymph nodes, thymus and spleen, with a dynamic interrelationship between the cells of these organs.

The role of hypoxia, infection and radiation on the bone marrow lymphocytes, as well as on the normoblasts and granular cells, is studied.

It is apparent from this work that normoblasts, granular cells and activated lymphoid cells confer protection to the organism in accordance with the number of cells injected, but small lymphocytes do not seem to protect against total body radiation.

The author also comments on the role of the lymphocyte in the production of antibodies. Antibody formation appears to represent a selective intensification of but one of many different cellular secretions, possibly associated with depression of other secretions. This is an unusual and highly adaptive form of specialization

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of the secretory function of the lymphocyte, which may be referred to as "conditioned secretion".

This book can be recommended to anyone interested in cytology but particularly to hematologists, experimental biologists and radiation workers.

THE CATARRHAL CHILD. John Fry. 139 pp. Butterworth & Co. (Publishers) Ltd., London; Butterworth & Co. (Canada) Ltd., Toronto, 1961. $5.00.

In his preface, the author says that he writes as a normal family doctor, but no one would consider Dr. John Fry an ordinary doctor, possessing as he does postgraduate degrees in both medicine and surgery and ample evidence of a more than average interest in learning. At the same time he is a member of the Council of the British College of General Practice and was one of the founder members of that organization. His claim to the title of family doctor is thus indisputable.

The material in this book is essentially clinical, being a review of the author's own experience over a ten-year period of careful follow-up involving 750 children. The common respiratory problems of childhood are represented—coughs and colds, otitis media, the wheezy chest, disorders of the adenoids and tonsils and other acute throat infections. Each disease has a separate chapter in which the etiology, treatment and prognosis are discussed and relevant statistics are extensively quoted. These statistics may at first be a little muddling to readers from the Americas who are not familiar with the Social Class method of study so commonly used in England. However, the references are clear and easily found and will repay examination. A short chapter on the use of antibiotics follows, and a review of general management ends the book.

The evident value of careful and methodical recording of what might at first seem dull and uninteresting should do much to encourage a similar approach by other family doctors. The greatest value of this book is that it will give perspective to students, family doctors and consultants—all of whom too often see things only from their own point of view. It encourages a self-critical attitude and would fill a gap in medical education for the student about to leave hospital for general practice. This book is recommended for reading by all final-year students.

A MINORITY. A Report on the Life of the Male Homosexual in Great Britain. Gordon Westwood. 216 pp. Longmans, Green & Company, Toronto, 1960. 30s. net.

This is an extensive study of 127 male homosexuals. It is particularly valuable because the sample was obtained from those who were not in difficulty with the law or in psychiatric treatment. In this way, the sample is more likely to be representative of the average male homosexual than most studies which have involved these two sub-groups. The study was designed not to test hypotheses but to accumulate factual information, from which other investigators and clinicians can classify, analyze and suggest hypotheses and theories. The author, thereby, has made an outstanding contribution to this problem.

The author has grouped his findings into sections on backgrounds, early homosexual experiences, attempts to combat, the extent of homosexual acts, heterosexual interests, sexual adjustment, the legal aspects, work and leisure, and community integration.

Nearly three-quarters of the subjects studied came from homes where both parents were present until at least the time when the homosexual attained the age of 15; half came from reasonably happy homes; some did have mothers who were possessive and overprotective and came from homes where the father was either absent or where the child/father relationship was poor; 80% were either the only son or the youngest son; most obtained their knowledge about sexual matters in a haphazard way.

Homosexual relations were first experienced by 81% before they were 16 and half of these were with boys of the same age; the first homosexual experience was usually no more than childhood sexual play; their histories did not show that education by an adult had any appreciable effect on the development of homosexual tendencies.

Forty per cent did not ask for any help or advice because of fear or embarrassment. Of those who did, most went to doctors other than their own family doctor. Nineteen per cent received treatment of some kind, mostly by psychiatrists. Fifty-nine per cent expressed no desire to change their homosexual tendencies. It was considered that 88% had adjusted themselves to their condition.

There was no evidence to support the view that homosexuality is on the increase. Eighty-one per cent of homosexual activities took place in private; 17% of homosexuals had some feminine mannerisms or characteristics; most homosexuals deplored femininity in homosexual behaviour.

Nearly two-thirds had not found any girl to be sexually attractive at any period of their lives. Some were able to marry.

Sixty-seven per cent were promiscuous, but 23% had relationships with one partner only.

Eighty per cent had never come into contact with the law for any reason.

Thirteen per cent had been threatened with blackmail; 30% had been robbed by homosexuals or men posing as homosexuals; 10% had been assaulted.

Less than 1% were exclusively interested in boys under 16; however, the dangers of child molestation from homosexuals is small but not negligible.

The individuals studied comprised a heterogeneous group of personality types. It was estimated that there are three-quarters of a million male homosexuals in England, and probably as many female homosexuals.

This book is a welcome addition to the psychiatric and social literature, and is highly recommended.

CHEMISTRY AND THERAPY OF CHRONIC CARDIOVASCULAR DISEASE. A Monograph in The Bannerstone Division of American Lectures in Living Chemistry. Richard J. Jones and Louis Cohen. 200 pp. Charles C Thomas, Springfield, Ill., 1961. $7.50.

This monograph presents in a very concise form some of the chemistry of congestive heart failure, thrombosis, atherosclerosis, and the modern concepts of serum lipid alterations.

The subjects dealt with are clearly presented in a somewhat didactic manner, but at the end of each section an extensive bibliography is provided which gives adequate and up-to-date references. These should be very useful to any student who wished to delve further into the topics discussed.

This book can be recommended to students and internists who want a quick review of the concepts of these particular aspects of internal medicine.

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NOTICE OF NATIONAL CANCER INSTITUTE OF CANADA RESEARCH FELLOWSHIPS

The National Cancer Institute of Canada offers a number of Research Fellowships. They are designed to provide advanced training and experience in cancer research for individuals who plan a career in which furthering knowledge about cancer will be a major interest. These Fellowships are not awarded for the purpose of providing practical clinical training (Clinical Fellowships are provided by the Canadian Cancer Society).

Fellowships are open on equal terms to men and women and are awarded to the applicants who are deemed best qualified on the evidence submitted.

A candidate must be a graduate of a university approved by the Institute. Research Fellowships are normally tenable in Canada.

The value of Fellowships will depend on the training and experience of the candidate.

Tenure and payment of a Fellowship will normally commence on April 1 or July 1.

Application for a Fellowship must be made by the candidate to the National Cancer Institute of Canada on an official form on or before December 15 of the preceding year.

A copy of the regulations concerning these Fellowships together with application forms may be obtained from the National Cancer Institute of Canada, 790 Bay Street, Toronto, Ontario.

VAN METER PRIZE AWARD FOR 1962

The American Thyroid Association, Inc. again offers the Van Meter Prize Award of $500.00 to the essayist submitting the best manuscript of original and unpublished work concerning "Goitre —especially its basic cause". The studies so submitted may relate to any aspect of the thyroid gland in all of its functions in health and disease. The award will be made at the Annual Meeting of the Association at the Roosevelt Hotel, New Orleans, Louisiana, U.S.A., May 9 to 12, 1962. A place on the program will be reserved for the winning essayist. When more than one author's name appears on the manuscript, the authors will be asked to designate a single recipient to receive the award.

The competing essays may cover either clinical or research investigations, should not exceed 3000 words in length and must be presented in English. Duplicate, typewritten copies, double-spaced, should be sent to the Secretary, Theodore Winship, M.D., 430 N. Michigan Ave., Chicago 11, Ill., U.S.A., not later than January 1, 1962.

OXYGEN CHAMBER FOR CANCER TREATMENT

A high-pressure oxygen chamber for use in the radiation treatment of cancer patients has been developed by three University College Hospital (England) doctors. Patients are placed in the Perspex chamber of the unit, which contains only pure oxygen, and the pressure is raised to four atmos-

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pheres. The potentially harmful effects of oxygen poisoning, which can include convulsions, are avoided by means of a special mechanical valve which allows the pressure to be built up very rapidly.

It is known that cells are more susceptible to damage when irradiated in the presence of oxygen. Accordingly, the patient's cells are steeped in the gas by the high pressure, then bombarded by the radiation. Such bombarding has been standard practice for many years, usually from radioactive cobalt or cesium sources. It is hoped that the new machine will make this treatment more effective.

The irradiation source is a 2000-curie cobalt unit, especially designed for use with the chamber.

The chamber can also be used in the treatment of other conditions, such as carbon monoxide poisoning and certain bacterial infections which respond to treatment with high-pressure oxygen. A smaller version of the chamber can be used for infants.

HISTOPLASMOSIS AS CAUSE OF LUNG CALCIFICATIONS

A high correlation between calcifications of the lung and histoplasmosis was found in a study undertaken at a Veterans Administration hospital in Tennessee, an area in which the fungus-caused pulmonary disease is endemic.

J. D. Mashburn, D. F. Dawson, and J. M. Young of the Veterans Administration Medical Teaching Group Hospital, Memphis, report on the study in a recent issue of *The American Review of Respiratory Diseases*, 84: 208, 1961.

Calcified pulmonary lesions were found in 100 of 111 autopsies, or 90%, and evidence of *Histoplasma capsulatum* could be detected in 71, or 63.9% of the cases. In 35 of the 100, there were splenic calcifications also, with organisms resembling the fungus. Almost all of the subjects had lived within the Mississippi Valley area and the majority resided in the area surrounding Memphis, or the "mid-South".

Thirty-seven of the 100 had "indoor" occupations, 37 had "outdoor" occupations not of an agricultural nature, and 26 were employed in an agricultural occupation. Of the "indoors", 27 were recorded as positive for Histoplasma organisms, as were 27 of the "outdoors", and 17 of the 26 with agricultural occupations.

"It should be understood that the lack of correlation between the incidence of organisms found in the occupation of the individual in no way contradicts previous studies showing the high incidence of *Histoplasma capsulatum* organisms found in such agricultural environments as chicken yards and rotting tree stumps," state the authors. "It should be kept in mind that most males of this general age group (World War I and World War II veterans) from this region have most likely had intimate contact with an agricultural environment at some period in their lives. The disease certainly may be contracted after very short exposure in an area where the soil contains the mycelial phase of the organism."

INTERPHALANGEAL OSTEOARTHRITIS

Crain (*J. A. M. A.*, 175: 1049, 1961) has drawn attention to a form of chronic, progressive osteoarthritis affecting the interphalangeal joints of the fingers, which, while not rare, has not previously been clearly delineated. It is characterized by periodic acute inflammatory episodes and sometimes considerable deformity and impairment of function may eventually occur in certain of the affected joints.

The clinical features of this disorder, as summarized from the author's experience with 23 cases, are that it occurs predominantly in middle-aged women, tends to be hereditary and is not infrequently accompanied by osteoarthritic changes in the cervical spine. The acute episodes often suggest rheumatoid arthritis, but the disease does not commonly affect other peripheral articulations. The erythrocyte sedimentation rate is only inconstantly elevated, and the various serological tests for rheumatoid factor are characteristically negative.

The results of treatment are generally unsatisfactory, although symptomatic relief is obtained in some cases by intra-articular hydrocortisone injections.

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SPECIAL PROGRAM FOR RESEARCH GRANTS IN RADIOLOGICAL HEALTH

In view of the rapid expansion which is forecast in the use of nuclear energy, x-rays, and other sources of radiation, a greatly expanded program for research grants in the field of radiological health has been developed by the Public Health Service Division of Radiological Health of the U.S.A. These grants are offered to support research by individuals, universities, hospitals, laboratories, and other public or private institutions in the assessment and control of man-made and natural radiation exposures to the individual, no matter how the separate components may originate. The knowledge and skills of many professional disciplines and specialties—physicians, engineers, physicists, chemists, educators, statisticians among them—are needed to find answers to the many challenging questions in radiological health.

Research proposals should contribute to the determination of the extent and character of the radiation problem as well as the mechanisms by which radiation produces damage. Studies aimed at the elucidation of the radiation damage "cause and effect" relationship are essential if low-level and long-term radiation exposure effects are to be accurately assessed and general control programs organized. Therefore, basic studies relating to critical body organs and systems, preferred metabolic pathways for specific radioactive contaminants, and an understanding of the radiosensitizing and modifying effects of various materials are encouraged.

Broad epidemiological studies aimed at a scientific evaluation of the long-term effects such as ageing, congenital malformations, genetic effects, behavioural patterns and cancer induction, are also of primary concern. Field studies of the movement of radioactive contaminants in biota and human food chains are of special interest, since we know that the physical environment may be greatly altered by biological activity, as for example, the concentration of water-borne radionuclides in micro-organisms and fish.

Purely physical studies, such as chemical mechanisms in radiation chemistry, the design of equipment and the development of techniques to accurately assess or reduce the population dosages are mandatory for a successful research program.

Studies aimed at directing scientific findings toward control devices or procedures are necessary in a "total view" of man's ecological system, as are studies that attempt to assess the relationship between health hazards created and possible benefits derived by radiation usage. The determination of the consequences of radiation exposure for present and future generations will require intensive investigation.

For information and/or application forms please contact: Dr. Paul F. Hahn, Chief, Office of Extramural Grants, Division of Radiological Health, U.S. Public Health Service, Washington 25, D.C., U.S.A.

COURSE IN LARYNGOLOGY AND BRONCHOESOPHAGOLOGY

The Department of Otolaryngology, University of Illinois College of Medicine, will conduct a postgraduate course in Laryngology and Bronchoesophagology from April 2 to April 14, 1962, under the direction of Dr. Paul H. Holinger.

Registration will be limited to 15 physicians who will receive instruction by means of animal demonstrations and practice in bronchoscopy and esophagoscopy, diagnostic and surgical clinics, as well as didactic lectures.

Interested registrants should write to the Department of Otolaryngology, University of Illinois College of Medicine, 1853 West Polk Street, Chicago 12, Ill., U.S.A.

INFLUENZA AND PNEUMONIA TRENDS IN U.S.

The death rate from influenza and pneumonia in the last four years has been adversely affected by widespread outbreaks of influenza, although mortality from these diseases seems currently on the downswing, the statisticians of the Metropolitan Life Insurance Company report.

The first outbreak of Asian influenza swept the country in the last quarter of 1957, with a second but less severe wave in the early months of 1958. As a consequence, the combined death rate from influenza and pneumonia in 1957 rose to 36 per 100,000 population—highest in a decade. The rate fell slightly in 1958 and again in 1959, but in 1960 the rate exceeded even the 1957 record because of another major outbreak of influenza in the first quarter of the year.

Provisional data for the first quarter of 1961 show a reversal of the trend once more. The influenza and pneumonia death rate for the first three months of 1961 was 38.3 per 100,000 compared with 65.5 for the same period last year, a decrease of two-fifths.

During 1957-58, the latest years for which detailed information is available, each age group recorded a rise in mortality from pneumonia and influenza compared with 1954-55 when the rates were at an all-time low. Of special significance was a 50% increase among white men in the age range 55-74 years. Despite the differences in the levels in the two periods, males had a higher death rate than females at almost every age. Among white women, by far the largest relative rise in the death rate occurred at ages 15-34 years, which include the main childbearing period.

The recent influenza outbreaks also appear to have influenced unfavourably the death rate from some other diseases, especially cardiovascular-renal conditions. It was estimated, in fact, that the excess number of deaths from these conditions, alone, was greater than those from pneumonia and influenza.

During 1957 - 60, the actual mortality from all causes in the United States exceeded by approximately 86,000 the number expected. About half this total was accounted for by the cardiovascular-renal diseases, and one-third by influenza and pneumonia. More than two-thirds of the excess deaths were among people at ages 65 and over.

HEALTH HAZARDS IN THE PLASTICS INDUSTRY

Plastics are a large and varied group of materials which consist of, or contain as an essential ingredient, a substance of high molecular weight which, while solid in the finished state, at some stage in its manufacture is soft enough to be formed into various shapes, most usually through the application either singly or together of heat and pressure. Most plastics are produced by synthesis from such natural resources as water, air, coal, salt, natural gas, etc. From these are derived the various chemicals and gases which are combined to produce the plastics materials. An article in the *Occupational Health Bulletin* (Vol. 16, 1961) describes one important member of the group, the epoxies, which are thermosets, and it discusses the hazards associated with their manufacture.

Many combinations and many different materials are thus possible; however, only one very important group, the epoxies, are discussed. The thermosets, as the term implies, set or harden (cure) under heat into a permanent shape. An irreversible chemical reaction called cross-linking occurs; this reaction links the resin chains so that the moulded piece is essentially one giant three-dimensional molecule. Subsequent heating, though it may soften the structure somewhat, cannot restore flow-ability that typifies the uncured resin. In this classification are such basic family groups as the amines, most polyesters, alkyds, epoxies and phenolics.

In Canada over 1000 companies do plastics fabrication and they are spread among a variety of industries. Sales of the plastic products industry, which is made up of 245 companies, were estimated at $83 million in 1960. This is, of course, not the total production. Many companies such as boat manufacturers and wire and cable extruders who use similar processes are classified as other industries. Such other production was estimated at $122 million in 1960.

The epoxy resins are somewhat toxic, since tertiary and tetra-amines released during the uncured, or wet, state cause allergic reactions in almost all personnel exposed. The epoxy resins are therefore an industrial hygiene problem that, unless non-toxic hardeners are developed, can be expected to increase as these resins come into wider and wider use. It has been generally stated that the polymerized "hardened" resin has little or no physical activity upon the skin or mucous membranes. It has been suggested in Great Britain, however, that tooling operations on hardened resin will give rise to decomposition products which are irritating to skin and mucous membranes. The nature of these decomposition products is not fully understood but is thought to include depolymerized resin, free amines and other intermediates.

Some epoxy resins are irritants, or sensitizers, or both, but the major problem in handling these materials occurs from the di- or tri-amine curing agents which are, for the most part, irritants and sensitizers. Dermatitis, therefore, is the most common effect experienced from exposure to epoxy resins although ill effects from inhalation of fumes of overheated plastic can

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also occur. There have been complaints that contact with the fumes has caused not only a dermatitis of the face, eyelids and neck, but also asthmatic symptoms from breathing the amine-contaminated air. Six cases of illness characterized by upper respiratory irritation and abnormal urinary findings occurring in workmen who were engaged in the destructive removal of epoxy resin concrete have been reported recently.

After the introduction of epoxy resins into industry, a large number of cases of contact dermatitis occurred. Many of the basic epoxy resins can be handled without irritating the skin, but most of the amines used as hardeners have an irritant or sensitizing effect. It is possible to avert contact dermatitis while working with epoxy resins by educating management, supervisory personnel, and workmen about the hazards associated with these materials; . .by introducing vapour and dust control measures, and by employing personal protective devices, notably protective gloves and adequate washing facilities and cleansing agents.

ANNOUNCEMENT OF OPHTHALMOLOGY COURSE

"Diseases of the Cornea", the major ophthalmology course presented by University of California Continuing Education in Medicine and Health Sciences, will begin December 7, 1961, at the U.C. Medical Center. The three-day program will incorporate the 16th Annual Proctor Lecture, to be delivered on Friday, December 8, by James Allen, M.D., professor of ophthalmology, Tulane University School of Medicine. The lecture topic will be "Methods of Production of Tissue Damage by Micro-Organisms'".

Michael J. Hogan, M.D., professor of ophthalmology and chairman of the department, U.C. School of Medicine, is chairman of the program. Other U.C. faculty members participating in the conference are Ernest K. Goodner, M.D., clinical instructor in ophthalmology and junior research ophthalmologist, Francis I. Proctor Foundation; Samuel J. Kimura, M.D., associate professor of ophthalmology and vice chairman of the department; William K. McEwen, M.D., associate professor of biochemistry, department of ophthalmology, and associate research biochemist, Francis I. Proctor Foundation; William H. Spencer, M.D., clinical instructor in ophthalmology; and Phillips Thygeson, M.D., professor of ophthalmology and director, Francis I. Proctor Foundation.

Conference topics are "Anatomy and Physiology of the Cornea and Limbus", "Laboratory Methods of Diagnosis", "Keratitis Secondary to Conjunctivitis", "Bacterial Ulceration", "Mycotic Ulceration", "Viral Keratitis", "Endogenous Corneal Disease", "Allergic Corneal Disease", "Corneal Dystrophies", "Tumours of the Limbus and Cornea", "Medical Treatment of Corneal Disease", and "Surgical Treatment of Corneal Disease".

Further information and registration forms may be obtained from Continuing Education in Medicine, University of California Medical Center, San Francisco 22, Calif., U.S.A.